AWARD NUMBER: W81XWH-13-1-0297

TITLE: Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back

PRINCIPAL INVESTIGATOR: Michael Beattie, PhD

CONTRACTING ORGANIZATION: University of California, San Francisco
San Francisco, CA 94103

REPORT DATE: December 2017

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Dec 2017	Final	30 Sep 2013 - 29 Sep 2017

4. TITLE AND SUBTITLE

Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-13-1-0297

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Michael S. Beattie, Ph.D.

E-Mail: michael.beattie@ucsf.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, San Francisco
1855 Folsom St, Ste 425
San Francisco, CA 94103

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Early management of blood pressure (BP) may be critical to outcome after spinal cord injury (SCI), but evidence-based protocols are needed. Optimal early treatment and management of SCI has not been established in clinical practice, nor in animal models. Guidelines for management of BP in acute SCI have been influenced by evidence of a relationship between hypotension and poor outcomes in TBI, and the aim of maintaining cerebral blood flow in thenface of increased intracranial pressure (ICP), but doubt remains about what is best for SCI. This grant focuses on the following two hypotheses: 1) Episodes of low BP (measured by mean arterial pressure (MAP) and systolic BP) in the early management of clinical SCI predict worse long-term functional outcomes, and 2)spontaneous hypotensive episodes in the perioperative period of experimental SCI in rats will result in worse outcomes. Both clinical data and experimental modeling studies address these specific hypotheses.

15. SUBJECT TERMS

Spinal cord injury, blood pressure, acute care

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	109	19b. TELEPHONE NUMBER *(include area code)*

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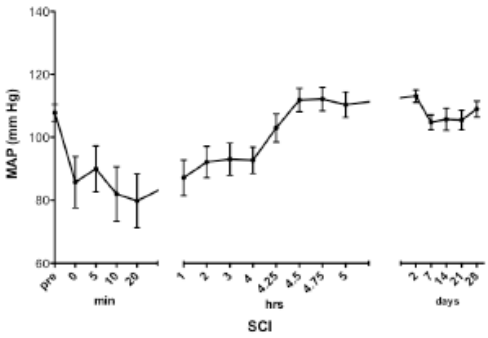
1. Introduction.
Early management of blood pressure (BP) may be critical to outcome after spinal cord injury (SCI), but evidence-based protocols are needed. Optimal early treatment and management of SCI has not been established in clinical practice, nor in animal models. Guidelines for management of BP in acute SCI have been influenced by the rather clear evidence of a relationship between hypotension and poor outcomes in TBI, and the aim of maintaining cerebral blood flow in the face of increased intracranial pressure (ICP), but doubt remains about what is best for SCI. This grant focuses on the following two hypotheses:
1) Episodes of low BP (measured by mean arterial pressure (MAP) and systolic BP) in the early management of clinical SCI predict worse long-term functional outcomes, and 2) spontaneous hypotensive episodes in the perioperative period of experimental SCI in rats will result in worse outcomes. Both clinical data and experimental modeling studies addressed these specific hypotheses.

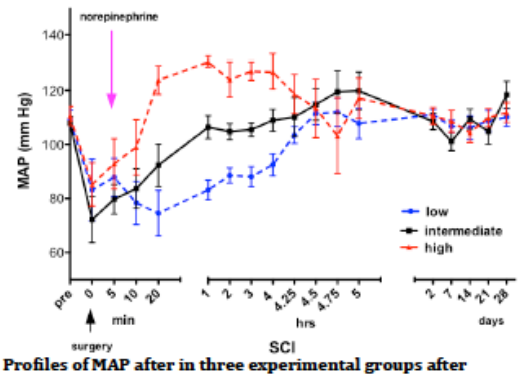
2. Keywords: Spinal Cord Injury, Acute care, Autonomic outcomes, Sensorimotor function

3. Accomplishments

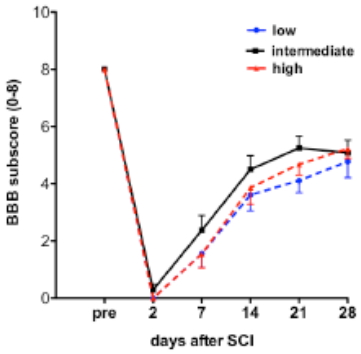
1. UCSF Animal Protocol and ACURO Protocol approvals were received for the animal study of blood pressure effects on outcome after spinal cord injury in the rat.
2. Human Subjects Protocol approval for the retrospective evaluation of spinal cord injury early critical care data were received from ZSFGH, Santa Clara Valley Medical Center and Palo Alto VA Health Sciences Center.
3. Human subjects protocol approvals for the prospective study of early critical care variables at UCSF-ZSFG were obtained.
4. Established 1) surgical methods for implanting Data Sciences blood pressure transducers in rats for telemetric monitoring of blood pressure in rats, and 2) the drug delivery techniques for holding blood pressure (BP) at specified levels for 4 hours after SCI in rats. We obtained data on rats sustaining 250 kilodyne impact at T3. BP, heart rate (HR), bladder function and locomotor function was assessed for 4-6 weeks after injury. A new approach to catheterizing the tail vein using a stylet and small diameter catheter was developed for this study. Isoflurane concentration was maintained at about 1.5% and norepinephrine was used to manipulate blood pressure. The results of this study are shown in the graphs in Figure 1 below, and indicates that both high and low blood pressure are predictive of poorer outcome; both locomotor and bladder function showed a significant effect. Interestingly, the amount of tissue sparing also reflected that the normotensive group had better outcome. These data are currently being prepared for publication.



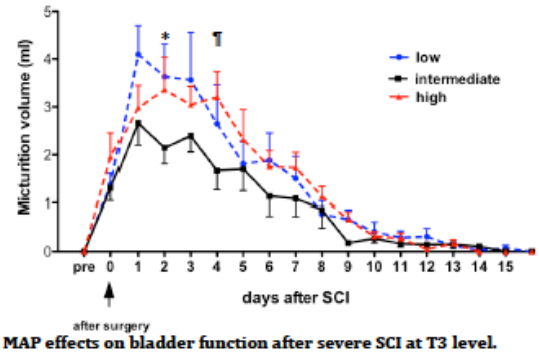
Profiles of MAP after spinal cord injury at T3 (250 Kdyne). Severe spinal cord injury at high thoracic spinal cord levels leads early hypotension. The decreased MAP is increased by 4 hr after injury. One Way ANOVA followed by Bonferroni's test, $p<0.0001$, $F_{17,216}=4.561$, N=13, *p<0.05, **p<0.001.



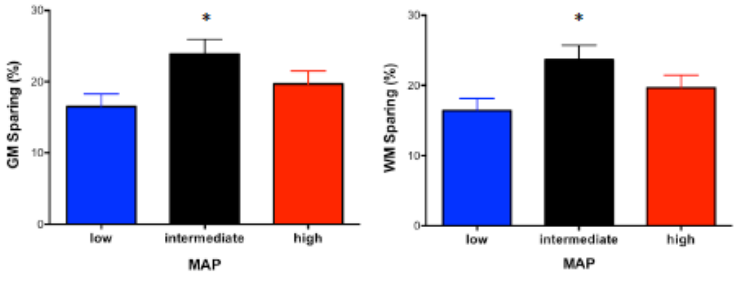
Profiles of MAP after in three experimental groups after severe SCI at T3 level. MAP was controlled by injecting norepinephrine after SCI for 4 hr after SCI. Three experimental groups were divided (low, MAP 70-90, n=9; intermediate, MAP 90-110, n=12; high, MAP 110-130, n=11). Two Way ANOVA followed by Bonferroni test, Interaction; $p<0.0001$, $F_{34,518}=2.56$, Treatment; $p<0.0001$. $F_{2,518}=23.05$. Time: $p<0.0001$. $F_{17,518}=8.08$.



MAP effects on motor functional recovery after severe SCI at T3 level. Intermediate, but not low or high, MAP leads better motor functional recovery after SCI over 4 weeks (low, MAP 70-90, n=9; intermediate, MAP 90-110, n=12; high, MAP 110-130, n=11). Two Way ANOVA, followed by Bonferroni test, Interaction; $p=0.9232$, $F_{10,174}=0.4$, Treatment; $p=0.0395$, $F_{2,174}=3.29$, Time; $p<0.0001$. $F_{5,174}=144.47$.



MAP effects on bladder function after severe SCI at T3 level. Intermediate, but not low or high, MAP leads better recovery in bladder function after SCI over 4 weeks (low, MAP 70-90, n=9; intermediate, MAP 90-110, n=12; high, MAP 110-130, n=11). Two Way ANOVA followed by Bonferroni test, Interaction; $p=0.5880$, $F_{34,521}=0.93$, Treatment; $p=0.0003$, $F_{2,521}=8.23$, Time; $p<0.0001$, $F_{17,521}=34.41$. Posthoc test; *P<0.05 (between low and intermediate),¶p<0.05 (between intermediate and high)



MAP effects on tissue damages after severe SCI at T3 level. Intermediate MAP, but not low or high, results better tissue sparing in gray and white matter. One Way ANOVA followed by Tukey's test. **Left)** gray matter sparing, $P=0.0409$, $F_{2,29}=3.575$. *p<0.05 compared to low. **Right)** White matter sparing, $P=0.0423$. $F_{2,29}=3.535$. *p<0.05 compared to low.

Figure 1.

5. Biweekly meetings were held with ZSFGH clinicians and basic scientists to work on analyzing data from ZSFGH patient records for the retrospective study. We were able to access the large existing database containing q 1min BP data from ZSFGH SCI patients from 2007-2013. This analysis showed that patients with more epochs of hypotension had poorer outcome. A manuscript describing this was published in Journal of Neurotrauma (Hawlryluk GWH, Whetstone W, Saigal R, Ferguson AR, Talbott JF, Bresnahan JC, Dhall SS, Pan J, Beattie MS, Manley GT (2015) Mean arterial blood pressures and duration of hypotension correlate with neurological recovery following human spinal cord injury: Analysis of high frequency physiologic data. J. Neurotrauma, 2015 Feb 10. PMID: 25669633. PMCID: PMC4677564.)
6. Once the access to the SCI patient data was established, we were able to evaluate MRI records as well. In collaboration with Dr. Jason Talbott of the Department of Radiology, a new MRI scoring system was established to use this information for prediction of injury severity in cervical injury. (See: Talbott JF, Whetstone W, Ready W, Ferguson AR, Bresnahan JC, Saigal R, Hawlryluk GWH, Beattie MS, Mabray M, Pan J, Manley GT, Dhall SS. (2015) The Brain and Spinal Injury Center (BASIC) spinal cord injury (SCI) score: A novel, simple, and reproducible method for assessing severity of acute cervical SCI using axial T2 MRI. J.Neurosurgery (Spine), 2015, 23:495-504. PMID: 26161519.) Also, novel statistical approaches to evaluating this type of data were developed. (See: Haefeli J, Mabray MC, Whetstone WD, Dhall SS, Pan JZ, Upadhyayula P, Manley GT, Bresnahan JC, Beattie MS, Ferguson AR, Talbott JF. Multivariate Analysis of MRI Biomarkers for Predicting Neurologic Impairment in Cervical Spinal Cord Injury. Am J Neuroradiol. 2016 Dec 22. PMID: 28007771.) A similar analysis was performed for evaluation thoracic and lumbar injury. (See: Mabray MC, Talbott JF, Whetstone WD, Dhall SS, Phillips DB, Pan JZ, Manley GT, Bresnahan JC, Beattie MS, Haefeli J, Ferguson AR. Multidimensional analysis of MRI predicts outcome in thoracic and thoracolumbar spinal cord injury. J Neurotrauma, 2015 Sep 28. PMID: 26414451. PMCID: PMC4876497.)
7. Retrospective data analysis at ZSFGH has also identified complications with vasopressor usage in central cord injuries. (See: Readdy WJ, Whetstone W, Ferguson AR, Talbott JF, Inoue T, Saigal R, Bresnahan JC, Beattie MS, Pan J, Manley GT, Dhall SS (2015) Complications and outcomes of vasopressor usage in acute traumatic central cord syndrome. J. Neurosurgery (Spine), 23: 574-580.)
8. Work on parallel blood pressure evaluations in animals and correlation with outcome using novel methods for data evaluation (topological data analysis) has been performed (Nielson, J, Paquette J, Liu AW, Guandique CF, Inoue T, Irvine KA, Gensel JG, Petrossian TC, Lum PY, Carlsson GE, Manley GT, Beattie MS, Bresnahan JC, Ferguson AR. Big-data visualization for translational neurotrauma: Topological data analysis for discovery in

preclinical spinal cord injury and traumatic brain injury. Nature Communications, 2015, 6:8581.)

9. Retrospective data analysis also showed that penetrating injuries have a different profile, in that attainment of MAP goals did not appear to affect outcome. However, this was a small study. (See: Readdy WJ, Saigal R, Whetstone W, Ferguson AR, Talbott JF, Inoue T, Bresnahan JC, Beattie MS, Pan JZ, Manley GT, Dhall SS (2016) Failure of mean arterial pressure goals to improve outcomes following penetrating spinal cord injury. Neurosurgery, 79: 708-714. (05.03.2016).doi: 10.1227/NEU.0000000000001249.)
10. A REDCap data acquisition system was developed for the prospective data collection at ZSFG and is currently being used. A summary of variables collected is in the appendix. This system was transferred Drs. Creasey and McKenna for use on retrospectively gathered data to implement procedures for accessing data from Santa Clara Valley Medical Center and Palo Alto VA Health Sciences Center. Intraoperative record data from ZSFGH and SCVMC have undergone preliminary analysis and shows that even for the time that patients were undergoing spinal cord surgery, there is an effect of low blood pressure. These data are currently being prepared for publication but have been presented as an abstract: Haefeli J, Torres D, Ehsanian R, McKenna SL, Suen CG, Nielson JL, Talbott JF, Manley GT, Whetstone WD, Dhall SS, Bresnahan JC, Beattie MS, Pan JZ, Ferguson AR (2016) Operating room autonomic measures as predictors of neurological outcome after spinal cord injury. Abstract, International Spinal Cord Society Meeting, Vienna, Austria.
11. The SCVMC group also has worked on respiratory function after SCI. This represents another important outcome measure related to critical care. A paper has been published: Zakrasek EC, Nielson JL, Kosarchuk JJ, Crew JD, Ferguson AR, McKenna SL (2017) Pulmonary outcomes following specialized respiratory management for acute cervical spinal cord injury: a retrospective analysis. Spinal Cord, **55**: 559-565.
12. A prospectively gathered data set on acute care of SCI patients at ZSFG was initiated the 3rd year of this project. (Follow-up data were collected during the one year no-cost extension.) The REDCap data collection system described above was used and the table below shows a partial data summary of patients admitted during the 3rd year of this grant. As can be seen from the Table 1, a total of 36 patients were enrolled in the study. We learned much from this first attempt to gather comprehensive data from these subjects. The experience gained has allowed us to improve so that the next cohort of patients supported under SC150177 is substantially more complete.

Table 1. Clinical Summary N=36 unless otherwise noted	Mean/Count (Range)
Demographics	
Total Patients Enrolled	36
Male	26
Age	49.6 (18-79)
Trauma Characteristics	
Level of Injury	
Cervical	20
Cervical-Thoracic	3
Cervical-Lumbar	1
Thoracic	6
Thoracic-Lumbar	3
Lumbar	2
Cervical-Thoracic-Lumbar-Sacrum	1
AIS at ED Admission	
A	8
B	5
C	2
D	6
Unable to Assess (sedated/altered mental state/etc)	16
Concurrent TBI Injury	6
Mechanism of Injury	
Fall	30
Transport	9
Assault	3
Crush Injury	1
Other	2
Blunt Injury	26
ISS on Arrival (N=19)	29.6 (10-75)
Central Cord	13
History of Hypertension	10
Hospital Stay	
Transport Time (N=25)	16.7 min (2-49)
Time in ED (N = 35)	229.74 min (48-782)
Time to OR (N=30)	10.9 hr (1.7-23.15)
ICU Length of Stay (N= 23)	9.6 Days (1.88-37.6)
Hospital Length of Stay (N= 23)	17.9 days (3.67-93)
Discharge (N= 33)	
Acute Rehab (N= 33)	21
Deceased (N= 33)	3
Nursing Home (N= 33)	2
Home/Private Residence (N= 33)	4
Group Living (N= 33)	1
Other Hospital (N= 33)	2
Follow Up	
# of 3Mo Phone Calls Completed	22
# of 6Mo In Person Visits Completed	16
# of 12Mo In Person Visits Completed	13

These data are currently being mined for relationships between autonomic variables and recovery.

4. Impact. Acute critical care for SCI has been guided mostly by clinical experience with a lack of evidence-based guidelines. The initial results of the current study have at the least affected the process by which guidelines for SCI acute care are determined at the Zuckerberg SFGH, and have provided new data on using physiological and imaging variables for predicting outcomes. This is driving the production of new treatment protocols here and across the SCI clinical community as we evaluate and disseminate our findings.

5. Changes/Problems. This study originally included 3 centers for acquiring retrospective data: ZSFG/UCSF, Santa Clara Valley Medical Center (SCVMC), and the VA Palo Alto Medical Center (VAPAMC). Our collaborators at SCVMC and VAPAMC, Drs. McKenna and Creasey, provided much expert input as we developed the RedCap database and implemented CDEs. SVCVMC also has provided data on respiratory therapies (Zakrasek et al, 2017) and on intraoperative MAP and outcomes (in progress), but was not able to provide as detailed acute care information as we had hoped, due in part to staffing issues and the complexities of sharing data. Much progress was made, however, and it is anticipated that SCVMC will participate in future collaborative studies. VAPAMC was not able to provide acute care data matched to longer term outcomes due to data transfer and restriction issues. Thus, VAPAMC withdrew from the study for year 3. They remain as collaborators and expert consultants.

6. Products. Products include the REDCap database structure (a summary is provided in the appendix), which includes NINDS CDEs along with multiple physiological and imaging variables. We have provided this data structure to SCVMC and VAPAMC, and to UCSF Fresno Medical Center. The data structure and definitions will be available to new centers as they join TRACK-SCI under SC150177. In addition, we produced the following publications, which are included sequentially in the appendix:

Dhall, S.S., J. Haefeli, J.F. Talbott, A.R. Ferguson, W.J. Readdy, J.C. Bresnahan, M.S. Beattie, J.Z. Pan, G.T. Manley, and W.D. Whetstone. 2017. Motor Evoked Potentials Correlate With Magnetic Resonance Imaging and Early Recovery After Acute Spinal Cord Injury. *Neurosurgery*. doi:10.1093/neuros/nyx320.

DiGiorgio, A.M., R. Tsolinas, M. Alazzeh, J. Haefeli, J.F. Talbott, A.R. Ferguson, J.C. Bresnahan, M.S. Beattie, G.T. Manley, W.D. Whetstone, P.V. Mummaneni, and S.S. Dhall. 2017. Safety and effectiveness of early chemical deep venous thrombosis prophylaxis after spinal cord injury: pilot prospective data. *Neurosurgical focus*. 43. doi:10.3171/2017.8.FOCUS17437.

Haefeli, J., M.C. Mabray, W.D. Whetstone, S.S. Dhall, J.Z. Pan, P. Upadhyayula, G.T.

Manley, J.C. Bresnahan, M.S. Beattie, A.R. Ferguson, and J.F. Talbott. 2017. Multivariate Analysis of MRI Biomarkers for Predicting Neurologic Impairment in Cervical Spinal Cord Injury. *AJNR Am J Neuroradiol*. 38:648–655. doi:10.3174/ajnr.A5021.

Hawryluk, G.W.J., W.D. Whetstone, R. Saigal, A.R. Ferguson, J.F. Talbott, J.C. Bresnahan, S.S. Dhall, J.Z. Pan, M.S. Beattie, and G.T. Manley. 2015. Mean Arterial Blood Pressure Correlates With Neurological Recovery Following Human Spinal Cord Injury: Analysis of High Frequency Physiologic Data. *J. Neurotrauma*. 32:1958–1967. doi:10.1089/neu.2014.3778.

Mabray, M.C., J.F. Talbott, W.D. Whetstone, S.S. Dhall, D.B. Phillips, J.Z. Pan, G.T. Manley, J.C. Bresnahan, M.S. Beattie, J. Haefeli, and A.R. Ferguson. 2015. Multidimensional Analysis of MRI Predicts Early Impairment in Thoracic and Thoracolumbar Spinal Cord Injury. *J. Neurotrauma*. 33:neu.2015.4093–962. doi:10.1089/neu.2015.4093.

Mabray, M.C., J.F. Talbott, W.D. Whetstone, S.S. Dhall, D.B. Phillips, J.Z. Pan, G.T. Manley, J.C. Bresnahan, M.S. Beattie, J. Haefeli, and A.R. Ferguson. 2016. Multidimensional Analysis of Magnetic Resonance Imaging Predicts Early Impairment in Thoracic and Thoracolumbar Spinal Cord Injury. *J. Neurotrauma*. 33:954–962. doi:10.1089/neu.2015.4093.

Nielson, J.L., J. Paquette, A.W. Liu, C.F. Guandique, C.A. Tovar, T. Inoue, K.-A. Irvine, J.C. Gensel, J. Kloke, T.C. Petrossian, P.Y. Lum, G.E. Carlsson, G.T. Manley, W. Young, M.S. Beattie, J.C. Bresnahan, and A.R. Ferguson. 1AD. Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury. *Nature Communications*. 6:1–12. doi:10.1038/ncomms9581.

Readdy, W.J., R. Saigal, W.D. Whetstone, A.N. Mefford, A.R. Ferguson, J.F. Talbott, T. Inoue, J.C. Bresnahan, M.S. Beattie, J. Pan, G.T. Manley, and S.S. Dhall. 2016. Failure of Mean Arterial Pressure Goals to Improve Outcomes Following Penetrating Spinal Cord Injury. *Neurosurgery*. 79:708–714. doi:10.1227/NEU.0000000000001249.

Readdy, W.J., W.D. Whetstone, A.R. Ferguson, J.F. Talbott, T. Inoue, R. Saigal, J.C. Bresnahan, M.S. Beattie, J.Z. Pan, G.T. Manley, and S.S. Dhall. 2015. Complications and outcomes of vasopressor usage in acute traumatic central cord syndrome. *J Neurosurg Spine*. 1–7. doi:10.3171/2015.2.SPINE14746.

Talbott, J.F., W.D. Whetstone, W.J. Readdy, A.R. Ferguson, J.C. Bresnahan, R. Saigal, G.W.J. Hawryluk, M.S. Beattie, M.C. Mabray, J.Z. Pan, G.T. Manley, and S.S. Dhall. 2015. The Brain and Spinal Injury Center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings. *J Neurosurg Spine*. 23:495–504. doi:10.3171/2015.1.SPINE141033.

Zakrasek, E.C., J.L. Nielson, J.J. Kosarchuk, J.D. Crew, A.R. Ferguson, and S.L. McKenna. 2017. Pulmonary outcomes following specialized respiratory management for acute cervical spinal cord injury: a retrospective analysis. *Spinal Cord*. 55:559–565. doi:10.1038/sc.2017.10.

7. Participants & Other Collaborating Organizations. As noted above, SCVMC and VAPAMC were collaborators on this translational partnership award. As the funding period ended, we were able to add the UCSF Fresno Medical Center to our consortium and they are now part of TRACK-SCI which is being supported by our current CDMRP award, SC150177.

8. Appendices.

Motor Evoked Potentials Correlate With Magnetic Resonance Imaging and Early Recovery After Acute Spinal Cord Injury

Sanjay S. Dhall, MD[*‡§]
Jenny Haefeli, PhD[*‡§]
Jason F. Talbott, MD, PhD[¶‡§]
Adam R. Ferguson, PhD[*‡‖§]
William J. Readdy, BS[*§]
Jacqueline C. Bresnahan, PhD[*‡§]
Michael S. Beattie, PhD[*‡§]
Jonathan Z. Pan, MD, PhD[‡#§]
Geoffrey T. Manley, MD, PhD[*‡§]
William D. Whetstone, MD[**§]

[*]Department of Neurological Surgery, University of California, San Francisco, San Francisco, California; [‡]Brain and Spinal Injury Center, San Francisco General Hospital, San Francisco, California; [§]Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI) Investigators, San Francisco, California; [¶]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California; [‖]Department of Neurological Surgery, SF-VA Medical Center, San Francisco, California; [#]Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California; [**]Department of Emergency Medicine, ZSFGH Emergency Center for Neuro-Critical Emergencies, San Francisco, California

Correspondence:
Sanjay S. Dhall, MD,
Department of Neurological Surgery,
University of California, San Francisco,
505 Parnassus Ave, Rm M-779,
San Francisco, CA 94143.
E-mail: sanjaydhall@gmail.com

Received, June 9, 2016.
Accepted, June 28, 2017.

BACKGROUND: While the utilization of neurophysiologic intraoperative monitoring with motor evoked potentials (MEPs) has become widespread in surgery for traumatic spine fractures and spinal cord injury (SCI), clinical validation of its diagnostic and therapeutic benefit has been limited.

OBJECTIVE: To describe the use of intraoperative MEP at a large level I trauma center and assess the prognostic capability of this technology.

METHODS: The SCI REDCap database at our institution, a level I trauma center, was queried for acute cervical SCI patients who underwent surgery with intraoperative monitoring between 2005 and 2011, yielding 32 patients. Of these, 23 patients had severe SCI (association impairment scale [AIS] A, B, C). We assessed preoperative and postoperative SCI severity (AIS grade), surgical data, use of steroids, and early magnetic resonance imaging (MRI) findings (preoperatively in 27 patients), including axial T2 MRI grade (Brain and Spinal Injury Center score).

RESULTS: The presence of MEPs significantly predicted AIS at discharge ($P < .001$). In the group of severe SCI (ie, AIS A, B, C) patients with elicitable MEPs, AIS improved by an average of 1.5 grades (median = 1), as compared to the patients without elicitable MEP who improved on average 0.5 grades (median = 0, $P < .05$). In addition, axial MRI grade significantly correlated with MEP status. Patients without MEPs had a significantly higher axial MRI grade in comparison to the patients with MEPs ($P < .001$).

CONCLUSION: In patients with severe SCI, MEPs predicted neurological improvement and correlated with axial MRI grade. These significant findings warrant future prospective studies of MEPs as a prognostic tool in SCI.

KEY WORDS: Spinal cord injury, Evoked potentials, Intraoperative monitoring, BASIC score

Neurosurgery 0:1–7, 2017 DOI:10.1093/neuros/nyx320 www.neurosurgery-online.com

While the utilization of intraoperative neurophysiologic monitoring (IOM) with somatosensoryevoked potentials (SSEP) and motor evoked potentials (MEPs) has become widespread in surgery for traumatic spine fractures and spinal cord injury (SCI), scientific studies of its diagnostic and therapeutic benefit have been limited. Several studies have demonstrated the value of IOM in spinal fusion and deformity, but there have been limited clinical studies documenting the use of IOM in spine trauma.[1,2] In particular, there is a paucity of data addressing the use of MEPs in this population. Given the anatomic basis of SSEPs and MEPs, it is generally accepted that SSEPs are more useful in the identification of posterior and dorsal column damage, while the utility of MEPs extends to the localization of anterior lesions in the motor aspect of the cord.[3,4]

This lack of clinical research is striking given that there is significant literature supporting the prognostic value of early neurophysiologic

ABBREVIATIONS: AIS, association impairment scale; **BASIC,** Brain and Spinal Injury Center; **EMG,** electromyography; **IOM,** intraoperative neurophysiologic monitoring; **MAP,** mean arterial pressure; **MEPs,** motor evoked potentials; **SCI,** spinal cord injury; **SSEPs,** somatosensory evoked potentials; **tcMEPs,** transcranial motor evoked potentials

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monitoring in preclinical models of SCI.[5,6] The few clinical studies that have documented intraoperative MEP use in traumatic spinal injury have not addressed the relationship between MEPs and clinical neurological function or recovery. Curt et al[7] showed a correlation between MEPs and neurological recovery in chronic SCI, but did not investigate the role of IOM, as their acute group received their first MEPs testing an average of 25 d post-trauma. Costa et al[8] found that epidural MEPs (D-waves) during early stabilization at an unclear time after injury were correlated with motor recovery.[8] Other studies have likewise examined the relationship between functional outcomes and MEPs, without examining the role of IOM. How intraoperative electrodiagnostic findings correlate with early imaging findings also remains largely unexplored in the setting of acute SCI.[9,10]

The purpose of this study was (1) to examine the relationship between MEP and clinical exam findings in acute SCI patients, (2) to assess MEPs for prognostic value in acute SCI, and (3) to explore the correlation between MEP and acute magnetic resonance imaging (MRI) findings.

METHODS

Study Design, Setting, and Participants

We performed a retrospective chart review to evaluate the diagnostic and prognostic value of MEPs for acute SCI patients admitted to a level I trauma center, between January 2005 and December 2011. The University Internal Review Board approved all research activities and the study was exempted from patient consent as it was classified as minimal risk. Patients were identified using a Department of Neurosurgery REDCap database of all spinal cord injuries/admissions and cross-referencing trauma logs, and searchable terms using electronic medical records. From this database, we retrospectively identified 131 patients with a principal diagnosis of SCI (code 953-957) according to the International Classification of Diseases, ninth revision, clinical modification, from codes designating discharge diagnoses. Of these patients, 32 met inclusion and exclusion criteria. All of these patients were cervical injuries. To be eligible, patients had to (1) be age $\geq$ 18, (2) have undergone surgical decompression utilizing intraoperative MEPs, and (3) have documented American Spinal Injury Association Impairment Scale (AIS) grading performed both at time of admission before surgery, as well as follow-up AIS grading (performed at time of patient discharge from acute care hospital). AIS grading was performed by SCI-trained physiatrists, neurosurgical, and neurocritical care physicians, and was selected as a measure of neurological outcome based on current guidelines for the classification of spinal cord injuries from the American Association of Neurological Surgeons/Congress of Neurological Surgeons.[11-13] AIS grades were obtained on all patients included in this study both before surgery and upon discharge. We excluded patients $<$ 18 yr of age, SCI related to penetrating trauma or imaging evidence for complete spinal cord transection.

Intervention Parameters: Imaging Workup and Initial Management

Twenty-seven patients underwent spine MRI prior to operative stabilization. MRI was performed on a 1.5 Tesla GE Genesis Signa scanner with imaging parameters as previously described (GE Healthcare, Milwaukee, Wisconsin).[14] Axial grading of MRI images was performed as previously described by Talbott et al,[14] utilizing the Brain and Spinal Injury Center (BASIC) score. All grading was performed by an attending neuroradiologist who was blinded to the clinical status of the patients. Briefly, based on the most severely affected axial T2 MRI image at the injury epicenter, grades were assigned as follows: grade 0 injury was defined as no cord signal abnormality, grade 1 injury was defined as T2 hyperintensity approximately confined to the gray matter, grade 2 injury was defined as T2 hyperintensity involving gray and some but not all of the white matter, grade 3 injury was defined as T2 hyperintensity involving the entire axial plane of the spinal cord, and grade 4 injury was defined as grade 3 injury with the addition of foci of T2 hypointensity consistent with macroscopic intramedullary hemorrhage.[14] Five patients were excluded from MRI analysis because they did not have an MRI performed prior to decompressive surgery.

Our institutional spinal cord perfusion clinical protocol was initiated with mean arterial pressure (MAP) goal of greater than 85 mm Hg based on the current recommendations for acute SCI.[15] Earlier in the course of this patient population, high-dose methylprednisolone was used at the discretion of the treating spine surgeon. Reflective of nationwide trends, steroids fell out of favor and were subsequently discontinued due to a lack of benefit and concern for deleterious effects.[16]

Intervention Parameters: Definitive Management

All patients underwent surgical decompression and instrumented stabilization, with a total of 32 surgical procedures in 32 patients. All surgeries were performed with IOM, including baseline MEP and SSEP prior to positioning and surgery.

Intervention Parameters: IOM

Cadwell Cascade Elite neuromonitoring equipment for neurophysiologic monitoring of transcranial electrically stimulated MEPs (tcMEPs), SSEPs, and free-running/evoked electromyography (EMG) were used (Cadwell Inc, Kennewick, Washington). For tcMEP monitoring, subdermal needle electrodes were placed in trapezious, deltoids, biceps, triceps, thenar, hypothenar, and foot flexor/foot extensor muscles bilaterally. Stimulation was carried out using a Cadwell TCS-1 double train stimulator (pulse with 50 ms, 2 trains of a total of 9 pulses, 1.7 ms interstimulus, interval 13.1 ms intertrain interval), constant voltage ranged from 100 to 1000 V. Transcranial stimulation was achieved using subdermal needle electrodes inserted at C1/C2. Anodal stimulation applied to C1 produced muscle responses in right-sided musculature, whereas anodal stimulation applied to C2 produced muscle responses in left-sided musculature. For EMG activity monitoring, subdermal needle electrodes placed for tcMEPs were used for cervical root monitoring bilaterally. A needle electrode in the right shoulder served as a ground. SSEPs/tcMEPs/EMGs were amplified using differential amplifiers (Cadwell Cascade), averaged and computer monitored (Dell, Round Rock, Texas). The anesthesia protocol used was propofol 120 mcg/kg/min, fentanyl 100 mcg/h with Sevoflurane 1.0% (0.5 MAC) and an MAP goal of $>$85 mm Hg was instituted given any concern for MEP integrity in low dose volatile anesthetics.[17]

Prepositioning baseline measures for both SSEPs and MEPs were established. Postprone position change baseline measures were also obtained. Final readings were taken with quantification/comments on significant changes in SSEPs/tcMEPs from baseline values. Two separate, blinded attending physicians independently evaluated whether MEPs

TABLE 1. Descriptive Demographics

Descriptive demographics Variable[a]	n = 32	MEP absent n = 13	MEP present n = 19
Male	26 (81.25)	10	16
Female	6 (18.75)	3	33
Mean age (yr)	57.4 ± 17.65	49.5 ± 16.6	63.1 ± 16.3 g
Mean MAP goals > 85 (h)	121.78 ± 41.9	135.5 ± 36.4	110.59 ± 43.60
Mean ISS score	22.83 ± 13.27	29.7 ± 16.9	19.4 ± 7.91
Steroids given	19 (59.38)	8	11
No steroids	13 (40.63)	5	8
Mean ICU LOS (d)	15.42 ± 19.39	26 ± 24.5	8.65 ± 5.928
Mean hospital LOS (d)	26.16 ± 26.81	33.92 ± 29.9	20.90 ± 21.45
Mortality	1 (3.33)	1	00

[a]Continuous variables reported as mean ± standard deviation; categorical variables reported as n (percent of total).

were present or absent based on the operating room Neurophysiologist's analysis of signal quality, communication to the surgeon, and reproducibility of waveforms. MEPs with weak signal were considered present as long as they were reproducible with a constant stimulation voltage.

Statistical Methods

All statistical analyses were performed in SPSS v.23 (SPSS Inc, IBM, Armonk, New York). We used a Mann–Whitney *U*-test to assess if early impairment (ie, AIS at discharge) differs between patients that had absent vs present intraoperative MEPs. In a next step, we tested if the amount of recovery in AIS grade is different between the patients with absent MEPs in comparison to the patients with present MEPs, (i) in the entire patient population and (ii) in a subpopulation of more severe SCI patients (ie, AIS A-C) using Mann–Whitney *U*-tests. The subpopulation analysis of the more severe SCI patients was done to address whether MEP analysis might be specifically useful in patients with more severe SCI, as patients having an initial AIS D grade are most likely to have preserved MEPs and have less room on the AIS scale to exhibit recovery (ie, a ceiling effect). Given that within our patient population the time to discharge was variable, we used an independent sample *t*-test to define if the hospital length of stay was different between the patients with absent MEPs in comparison to patients with present MEPs.

We used a Kruskal–Wallis test to assess if early impairment (ie, AIS at discharge) differs between patients having different axial grading of MRI images acquired prior to surgery (ie, BASIC score). In addition, we tested if intraoperative MEPs correlated with the BASIC scores using a Spearman correlation. Statistical significance for all tests was set at $\alpha = 0.05$.

RESULTS

Participants and Descriptive Demographics

The mean age in this cohort of patients was 57.4 (range 22-86 yr) and AIS grades at admission were A (n = 12), B (n = 5), C (n = 6), D (n = 9). Descriptive demographics for this cohort can be found in Table 1. Of note, approximately 19 of the 32 patients received high-dose methylprednisolone. There was no clear relationship between administration of high-dose methylprednisolone and MEPs or AIS recovery. All patients underwent surgical decompression and stabilization with intraoperative MEPs, this decompression occurred within 36 h for all patients.

Main Results

Patient change of AIS grades from admission to hospital discharge can be seen in Table 2. The presence of MEPs significantly predicted AIS at discharge ($P < .001$, Mann–Whitney *U*-test). Namely, patients with present intraoperative MEPs had higher AIS grades at discharge in comparison to patients with absent MEPs. When looking at the entire patient population (ie, initial AIS A-D grades), the amount of recovery in AIS grade was not significantly different between patients with absent MEPs in comparison with patients with present MEPs ($P = .158$, Mann–Whitney *U*-test). However, in the subgroup analysis that included the patients with more severe SCI (ie, AIS A-C), AIS recovery was significantly different between patients with MEPs vs patients without intraoperative MEPs ($P < .05$, Mann–Whitney *U*-test). In the group of severe SCI (ie, AIS A, B, C) patients with elicitable MEPs, AIS improved by an average of 1.5 grades (median = 1), as compared to the patients without elicitable MEP who improved on average 0.5 grades (median = 0). We were concerned that the variable time to discharge within the patient population might have caused this effect. However, the length of hospital stay of subjects with present intraoperative MEPs was not significantly different from the ones with absent MEPs (t [28] = 1.47, $P = .15$). The relationship between the presence and absence of intraoperative MEPs and AIS grade conversion is shown in Figure. All severe SCI patients (AIS A-C) that had present intraoperative MEPs converted at least 1 AIS grade from admission to discharge. In the patient cohort that did not have elicitable intraoperative MEPs (n = 13), 8 did not show any AIS grade conversion and 1 patient deteriorated from AIS B to A. There

TABLE 2. Incidence of recovery stratified by initial AIS grade

Variable[a]	Incidence of recovery stratified by initial AIS grade			
	AIS A (n = 12)	AIS B (n = 5)	AIS C (n = 6)	AIS D (n = 9)
1 grade improvement	0 (0)	2 (40.0)	5 (83.33)	3 (33.33)
2 grade improvement	3 (25.0)	1 (20.0)	1 (16.67)	0 (0)
3 grade improvement	1 (8.3)	0 (0)	0 (0)	0 (0)
4 grade improvement	1 (8.3)	0 (0)	0 (0)	0 (0)
No improvement or regression	7 (58.3)	2 (40.0)	0 (0)	6 (66.67)

[a]Categorical data reported as n (percent of total).

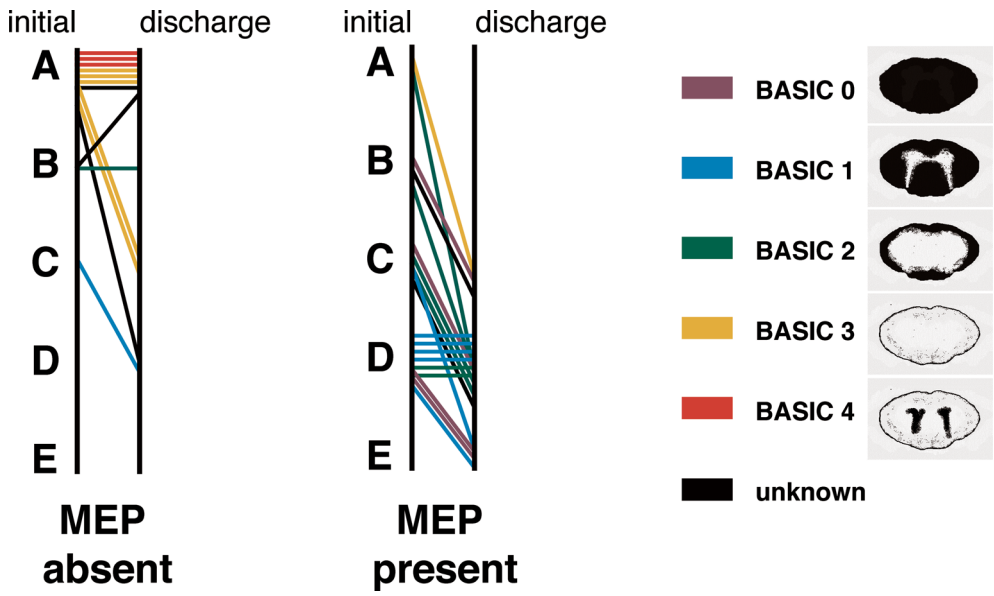

FIGURE. *Change in neurological status by MEP status and axial T2 MRI pattern (BASIC score). Crossover plots for all patients without (left) and with (middle) elicitable MEPs. Each patient on the crossover plots is also color-coded by their axial T2 MRI pattern (legend on far right). A black line indicates that MRI was not performed and axial T2 pattern is therefore unknown.*

was no significant difference in time to surgery for patients with or without MEPs. We then removed all AIS A patients from both groups, and performed another analysis of the remaining AIS B and C patients. Though the resulting group was too small for statistical analysis, we noted that AIS B and C patient without elicitable MEPs had zero AIS improvement as compared to a mean improvement of greater than 1 (1.25) AIS grade in AIS B and C patients with elicitable MEPs.

In addition to the intraoperative MEPs, MRI prior to decompression surgery using the BASIC score distinguished AIS at discharge grade (Kruskal–Wallis test, $P < .001$). Further, a correlation between MEP status and MRI findings was observed as patients with absent MEPs had significantly higher BASIC scores in comparison to the patients with present MEPs (Spearman's rho = –0.667, $P < .001$). In the patients with preoperative MRI and no elicitable MEPs, 8/10 (80%) had a high BASIC score (ie, BASIC 3 or 4; Figure). All patients that had a BASIC score of 4 did not change in their AIS grade from admission to discharge. This is consistent with data in Talbott et al,[14] who noted a lack of improvement in patients who had higher BASIC scores, particularly BASIC 4 which is associated with intramedullary hemorrhage. Among patients with intact MEP and preoperative MRI, 16/17 (94%) had low BASIC scores with evidence of varying degrees of spinal cord sparing (ie, BASIC 0-2; Figure).[14,18]

DISCUSSION

Key Results

In the present study, we have evaluated the prognostic value of IOM for predicting early neurological recovery after acute SCI. Specifically, we show that intraoperative MEP status (ie, present or absent) is highly predictive of AIS grade and AIS conversion in severe SCI at time of patient discharge. Further, we show strong electroradiologic correlation, as intraoperative MEP status is highly correlated with axial MRI grade (BASIC score), a radiological measure that has been previously shown to highly correlate with early neurological impairment in SCI.[14,18]

Interpretation

Tsirikos and colleagues[19] published their experience with 80 patients with cervical, thoracic, and lumbar traumatic fractures, who underwent surgical reconstruction utilizing intraoperative SSEP monitoring. Approximately half of these patients had incomplete SCI associated with their fracture, although they did not further specify the severity of the injury or an AIS grade. They did note a direct relationship between the degree of SSEP amplitude depression during surgery and postoperative neurological worsening. Along the same lines, they demonstrated that an improvement of 20% or greater in amplitude was correlated with postoperative improvement. They did not report the use of MEPs in this series.

Castellon and colleagues[20] reported a small series of 18 patients with thoracolumbar burst fractures who underwent surgical reconstruction utilizing intraoperative SSEPs and MEPs. The majority of these patients were reported to be neurologically intact, and 4 patients had a mild SCI of AIS D or better. They noted a decrease in the mean latency after spinal cord decompression. They did not draw any conclusions regarding the relationship between MEPs and recovery from SCI. Curt et al[7] evaluated magnetic MEPs after SCI at the 25-d mark and found them to be significantly related to the outcome of ambulatory capacity and hand function.

Talbott and colleagues[14] recently published a 5-point MRI grading scale (BASIC score) based on axial T2 images for acute cervical and thoracic SCI.[18] We applied this scale to our patients and noted that patients with elicitable MEPs had significantly lower BASIC scores ($P < .001$). MEP status tended to segregate patients into 2 basic MRI patterns. A majority of patients (80%) without elicitable MEPs had T2 signal abnormality that involved the entire transverse extent of the spinal cord (BASIC 3 and 4), while nearly all patients (94%) with preserved MEPs had varying degrees of relative spinal cord sparing on axial T2 MRI (BASIC 0-2). These findings emphasize the importance of preserved spinal cord white matter for neurological function as now supported with both electrodiagnostic and imaging modalities in the current study. We also confirmed results from multiple prior studies related to the strong negative prognostic finding of intramedullary hemorrhage.[21,22] In our cohort, patients with evidence for intramedullary hemorrhage on axial T2 (BASIC 4) did not recover. None of these patients had elicitable MEPs. These findings represent an important and novel electroradiologic relationship between MRI and intraoperative MEP in acute traumatic SCI and highlight the value of a multimodality diagnostic approach.

To date, there have not been any published studies that have attempted to correlate MEPs, MRI grading, and recovery after SCI. Thus, these findings are important. For example, the use of MEP in spine trauma may also provide prognostic value that can guide postoperative treatment as well as patient/family counseling. Finally, the significant relationship between MEPs and neurological status/recovery and early MRI findings may lead to expanded use of MEPs outside of the operating room. MEPs may have a role in the intensive care unit setting, and perhaps may even be used to guide medical management, such as MAP goals. Future studies are required to evaluate the use of MEPs in the intensive care setting.

Limitations

The authors acknowledge that there are limitations to this study. This is a retrospective chart review, and is subject to the biases inherent with such studies. This study utilizes AIS grades rather than International standards for neurological classifications of SCI scores, which were only recently adopted at our institution. We acknowledge that AIS grades provide less detailed information to evaluate postsurgical changes. Our AIS grades were obtained during the acute hospitalization. Length of stay can be confounding for a variety of reasons, many of which are not a reflection of clinical outcomes. In our institution, a number of patients lack basic resources and health insurance, and often spend variable amounts of time admitted for social and placement issues. We understand that there is not a simple way to resolve the possible impact of this on our study, but we did confirm that there was not a relationship between presence of MEPs and length of stay. Documented bulbocavernosus reflex was not available for this review; however, we are collecting this data prospectively. While this study establishes MEPs as an important tool for SCI prognostication, it does not prove the superiority of using IOM during spine trauma surgery. In these patients, who often have highly unstable traumatic spine injuries, this modality may help the surgeon reduce the risk of iatrogenic injury during positioning, open/closed reduction, and surgical decompression. Finally, the most compelling finding in this study is the relationship between elicitable MEPs and SCI outcome. However, this is limited by a relatively small number of patients (32 patients), and a prospective study with more patients and fixed time points of outcome assessment is warranted. In spite of these limitations, this study has successfully identified a robust relationship between MEPs and neurological outcome after SCI.

CONCLUSION

Successful intraoperative elicitation of MEPs appears to be strongly associated with at least partial sparing of spinal cord tissue on axial T2 MRI and with neurological recovery after SCI. Future studies of the role MEPs in the ICU setting are warranted, and perhaps they may even be used to guide medical management, such as MAP goals. Our study is the first to demonstrate electroradiographic correlation between intraoperative electrophysiologic data (intraoperative MEP status) and previously validated MRI measures of injury severity in acute SCI. This study represents a novel and significant finding of a relationship between MEPs and potential for recovery after SCI during the acute hospitalization. Present data warrant more extensive evaluation in a prospectively designed multicenter study, and perhaps the expansion of the use of MEPs outside of the operating room in acute SCI.

Disclosures

Partial support provided by Department of Defense CDMRP award SC120259 (MSB, GTM, JCB, WDW, ARF) and the Craig H. Nielsen Foundation (JH). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Long-held belief that traumatic spinal cord injury (SCI) patients do not recover neurologic function is being supplanted with emerging evidence that select individuals can have significant motor and sensory gains over time.[1,2] This improvement is attributed to promising single and multi-modal interventions including early surgical decompression, optimized spinal cord perfusion pressure, and early rehabilitation, among other more experimental approaches. This recognition begs the question – which individuals have the most potential for neurologic recovery (and therefore, may be best targeted for certain therapies)? Conversely, better understanding of the long-term likelihood of permanent neurologic disability has important implications with regards to chronic SCI care, complication management, as well as, healthcare and societal cost.

The study provides an encouraging approach for predicting possible neurologic recovery after traumatic SCI. Using intraoperative motor evoked potential (MEP) monitoring during early surgery (<36 hours) for cervical SCI, they observed that individuals with elicitable MEPs were more likely to improve in AIS grade compared to those without MEPs. This finding may seem intuitive. While, there were some AIS A patients with elicitable MEPs and eventual motor recovery, the fact is that more AIS A patients were in the no MEP cohort. This suggests that the absence of MEPs may simply be a marker for severity of AIS grade at presentation. It should also be noted that the admission AIS grade was documented without indicating presence of a bulbocavernosus reflex. It is possible that some presented in spinal shock, and therefore their admission AIS grade was not an accurate reflection of their true neurologic injury.

This study is an important step in understanding the evolving pathophysiologic milieu in acute traumatic SCI. It is evident that not all acute SCI individuals are to be relegated to a dismal prognosis. Hopefully with

further characterization of those with enhanced potential for recovery, protocols for patient-specific treatment can be best defined, implemented and studied for positive effect.

Daniel J. Hoh
Gainesville, Florida

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NEUROSURGICAL FOCUS

Neurosurg Focus 43 (5):E21, 2017

Safety and effectiveness of early chemical deep venous thrombosis prophylaxis after spinal cord injury: pilot prospective data

Anthony M. DiGiorgio, DO, MHA,[1,5] Rachel Tsolinas, BA,[2] Mohanad Alazzeh, BS,[3] Jenny Haefeli, PhD,[2] Jason F. Talbott, MD, PhD,[4] Adam R. Ferguson, PhD,[2] Jacqueline C. Bresnahan, PhD,[2] Michael S. Beattie, PhD,[2] Geoffrey T. Manley, MD, PhD,[5] William D. Whetstone, MD,[6] Praveen V. Mummaneni, MD,[5] and Sanjay S. Dhall, MD[5]

[1]Department of Neurosurgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana; [2]UCSF Brain and Spinal Injury Center, and [4]Department of Radiology and Biomedical Imaging, Zuckerberg San Francisco General Hospital, San Francisco; [3]David Geffen School of Medicine, University of California, Los Angeles; and Departments of [5]Neurological Surgery and [6]Emergency Medicine, University of California, San Francisco, California

OBJECTIVE Spinal cord injuries (SCIs) occur in approximately 17,000 people in the US each year. The average length of hospital stay is 11 days, and deep venous thrombosis (DVT) rates as high as 65% are reported in these patients. There is no consensus on the appropriate timing of chemical DVT prophylaxis for this critically injured patient cohort. The object of this study was to determine if low-molecular-weight heparin (LMWH) was safe and effective if given within 24 hours of SCI.

METHODS The Transforming Research and Clinical Knowledge in SCIs study is a prospective observational study conducted by the UCSF Brain and Spinal Injury Center. Protocol at this center includes administration of LMWH within 24 hours of SCI. Data were retrospectively reviewed to determine DVT rate, pulmonary embolism (PE) rate, and hemorrhagic complications.

RESULTS Forty-nine patients were enrolled in the study. There were 3 DVTs (6.1%), 2 PEs (4.1%), and no hemorrhagic complications. Regression modeling did not find an association between DVT and/or PE and age, American Spinal Injury Association grade, sex, race, or having undergone a neurosurgical procedure.

CONCLUSIONS A standardized protocol in which LMWH is given to patients with SCI within 24 hours of injury is effective in keeping venous thromboembolism at the lower end of the reported range, and is safe, with a zero rate of adverse bleeding events.

https://thejns.org/doi/abs/10.3171/2017.8.FOCUS17437

KEY WORDS spinal cord injury; DVT prophylaxis; low-molecular-weight heparin; spine trauma; thromboembolic events

Spinal cord injuries (SCIs) in the US have been on the rise, with an estimated yearly incidence of 17,000 cases.[13] Spinal cord injuries are most prevalent in middle-aged white males, with motor vehicle collisions as the most common cause.[8,13] Approximately 243,000–347,000 people in the US live with an SCI, with 30% hospitalized at least once a year after discharge. The initial length of acute hospitalization for SCIs is 11 days, with 35 days of rehabilitation.[10,13]

Deep venous thrombosis (DVT) and pulmonary embolism (PE) in SCI are common. Together these events are referred to as venous thromboembolism (VTE). Reported DVT rates in the literature are variable, as high as 65% in some studies.[4,12] The PE rates also have a variable reported range from 0% to 18%.[4,6,11,12] In a cohort study of the short-term and long-term risk of a VTE in 94 patients with SCI, it was found that most VTE complications occur within 3 months of the SCI.[5]

The 2013 SCI guidelines were published by the American Association of Neurological Surgeons/Congress of

ABBREVIATIONS AANS/CNS = American Association of Neurological Surgeons/Congress of Neurological Surgeons; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SCI = spinal cord injury; TRACK = Transforming Research and Clinical Knowledge; VTE = venous thromboembolism.

SUBMITTED June 30, 2017. **ACCEPTED** August 4, 2017.
INCLUDE WHEN CITING DOI: 10.3171/2017.8.FOCUS17437.

Neurological Surgeons (AANS/CNS) Joint Section on Disorders of the Spine and Peripheral Nerves. These guidelines give a Class I recommendation for low-molecular-weight heparin (LMWH) use for VTE prophylaxis and a Class II recommendation for starting within 72 hours of injury.[3]

Transforming Research and Clinical Knowledge in SCIs (TRACK SCI) is a prospective observational study based at the University of California, San Francisco. It introduced a standardized SCI treatment protocol and prospective data collection. The trauma protocol includes administration of LMWH (enoxaparin) within 24 hours of injury. The aim of the present study is to review the TRACK SCI data and determine if there is a reduction in VTE over established rates, as well as to evaluate the safety of early LMWH administration through assessment of adverse hemorrhagic events.

Methods

The TRACK SCI is a prospective observational study conducted by the UCSF Brain and Spinal Injury Center. This study recruited patients at Zuckerberg San Francisco General Hospital's Level I Trauma Center. Institutional review board approval was obtained at this site for all study procedures.

Patients were enrolled from May 2015 through March 2017. All English-speaking and non–English-speaking patients who presented to the emergency department and who were diagnosed with a traumatic SCI, whether blunt or penetrating, were initially eligible for the study. Patients who were younger than 18 years, in custody, prisoners, pregnant, or on medically evaluated psychiatric hold were excluded from the study. Informed consent was obtained for all patients.

The standard protocol for these patients involves initiating chemical DVT prophylaxis with LMWH (40 mg subcutaneous enoxaparin administered daily) within 24 hours of injury. Patients with SCI who undergo operation are taken for surgery within 24 hours of injury, and LMWH is withheld for 24 hours after surgery. Due to the nature of referral patterns in San Francisco, Zuckerberg San Francisco General Hospital does not receive trauma patients transferred from other institutions.

Data from the TRACK SCI database were reviewed. The DVT and PE rates were recorded along with any hemorrhagic complications. Patients did not undergo routine screening. Duplex ultrasound was performed if there was clinical suspicion for DVT or PE, and PE was confirmed with CT angiography. Multivariate regression modeling was performed using IBM SPSS (IBM Corp.).

Results

Of the 49 patients enrolled, 32 (65.3%) were male. The average age was 53.5 years, with a range of 18–49 years. The largest group of patients was Caucasian (38.8%, n = 19); followed by Asian (24.5%, n = 12); African American (18.4%, n = 9); and Hispanic (16.3%, n = 8), with only 1 patient who was "other" or declined to state (2%). The mean time from injury to emergency department arrival averaged 17 minutes. Complete SCIs were present in 9 patients (18.4%), and 40 (81.6%) underwent a spinal surgery. Seven patients (14.3%) had additional nonneurosurgical injuries. The average ICU stay was 8.6 days, and the average hospital length of stay was 15.9 days. Discharge dispositions were rehabilitation (36.7%, n = 18); nursing facility (20.4%, n = 10); home (14.3%, n = 7); and another acute care facility (20.4%, n = 10). A total of 4 patients (8.2%) died during their hospital stay. Of those who survived, only 1 patient had a neurological decline from presentation, which was later attributed to a cerebrovascular accident. See Table 1 for a summary of results.

There were 3 DVTs (6.1%), 2 PEs (4.1%), and no hemorrhagic complications (Table 2). Regression modeling did not find an association between DVT or PE and age, American Spinal Injury Association grade, sex, race, or having undergone a neurosurgical procedure ($p > 0.05$ for all variables).

Discussion

The existing literature does not provide clear data on when to start chemical DVT prophylaxis, and there is a great deal of caution among spine surgeons about the potential for hemorrhagic complications. In the current published literature, there is only 1 study that specifically examines the timing of chemical DVT prophylaxis. A prospective trial by Aito et al. compared patients presenting with acute SCI who received LMWH on hospital admission to their rehabilitation center. The admission window was between 72 hours of injury or after 8 days. Within the 72-hour cohort, 2% of patients developed a DVT on routine ultrasonography versus 26% of patients in the other cohort.[1] There were no adverse bleeding events in either group.

Other studies have specified time to chemical DVT prophylaxis, but have not directly compared differing times. A randomized controlled trial by the SCI investigators compared subcutaneous heparin to LMWH administered within 72 hours of SCI. They found a DVT rate of 63.3% in the subcutaneous heparin group versus 65.5% with LMWH, and a PE rate of 18.4% versus 5.2% for subcutaneous heparin versus LMWH, respectively.[12] A retrospective review by Harris et al. looked at LMWH started at admission after SCI. Not all of the patients in their group underwent surgery within 24 hours of injury, so for them the LMWH was started on admission, withheld 24 hours prior to the operation, and then restarted 24 hours after. There was no evidence of DVT; however, there were 3 episodes of bleeding complications that were attributed to the therapy.[9]

The recommended range of time to wait before starting chemical DVT prophylaxis varies widely. Ploumis et al. recommend starting LMWH within 2 weeks,[14] whereas Christie et al. recommend 72 hours.[2] The AANS/CNS Joint Section on Trauma and Neurocritical Care suggests starting LMWH for DVT prophylaxis within 72 hours.[3]

There is, similarly, a wide variation of DVT rates in the literature, due to a multitude of prophylaxis and screening methods. For example, Gündüz et al. found a 53.3% DVT rate with subcutaneous heparin prophylaxis and routine venography.[7] A meta-analysis by Furlan and Fehlings

TABLE 1. Demographics of the 49 patients with SCI prospectively tracked in this study

Factor	Value
Male sex	32 (65.3)
Race	
Caucasian	19 (38.8)
Asian	12 (24.5)
African American	9 (18.4)
Hispanic	8 (16.3)
Other/declined to state	1 (2)
Complete SCI on admission	9 (18.4)
Underwent spinal procedure	40 (81.6)
Additional nonneurosurgical injuries	7 (14.3)
Mean ICU stay in days, ± SD	8.59 ± 8.02
Mean hospital length of stay in days, ± SD	15.88 ± 15.47
Discharge disposition	
Rehabilitation	18 (36.7)
Nursing facility	10 (20.4)
Home	7 (14.3)
Acute care	10 (20.4)
Deceased	4 (8.2)

Values are expressed as the number (%) of patients unless otherwise noted.

found rates from 6% to 50%, and also concluded that routine DVT screening is not recommended.[4]

Few studies have examined the adverse bleeding rates after LMWH administration. The SCI investigators looked at 230 patients receiving enoxaparin within 72 hours of SCI. They had a 2.6% rate of major bleeding complications, 14.8% risk of minor bleeding complications, and, as mentioned above, DVT and PE rates of 65.5% and 5.2%, respectively.[12]

With our aggressive LMWH administration, the data show a 6.1% DVT and a 4.1% PE rate, with an absence of bleeding events. Although our thromboembolic event rate is higher than in the retrospective study by Harris et al.,[9] it is on the lower end of the commonly reported DVT rates in the literature. Our study's main significance comes with the absence of adverse bleeding events. This suggests that LMWH is safe if given within 24 hours of injury, as is done with our standard protocol.

The TRACK SCI is a prospectively collected SCI database. This makes our study unique in that it is based on prospectively collected data with a defined chemical DVT prophylaxis protocol. Although this is a retrospective review of the data, the standardized, prospective nature of the TRACK SCI data collection helps to minimize many of the inherent biases in retrospective chart reviews—notably selection bias. A limitation of this study is the relatively smaller sample size when compared with the retrospective reviews cited here.

TABLE 2. Thromboembolic events and hemorrhagic complications from aggressive LMWH therapy

Thromboembolic Event	No. (%)
DVT	3 (6.1)
PE	2 (4.1)
Hemorrhagic complications	0

Our data reiterate the prospective data found by Aito et al., that early LMWH is safe and can lower DVT rates substantially when given within 72 hours of SCI.[1] The other prospective study, by the SCI investigators, had a similar PE rate to ours; however, their routine DVT screening yielded a much higher DVT rate.[12] Furthermore, our early pilot data suggest that the common concern about hemorrhagic complications from prophylactic doses of enoxaparin may not be as substantial as once believed.

Conclusions

A standardized protocol in which LMWH is given to patients with SCI within 24 hours of injury is effective in keeping VTE at the lower end of the reported range, and is safe, with a zero rate of adverse bleeding events.

Acknowledgments

Partial support was provided by the Department of Defense Congressionally Directed Medical Research Program (CDMRP) award SC120259 (M.S.B., G.T.M., J.C.B., W.D.W., A.R.F.) and the Craig H. Nielsen Foundation (J.H.).

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Disclosures

Dr. Dhall reports being a consultant for DePuy Spine. Dr. Mummaneni reports being a consultant for DePuy Spine and Stryker Spine; receiving honoraria from Globus and AOSpine; having direct stock ownership in Spinicity ISD; receiving royalties from DePuy Spine, Springer Publishing, and Thieme Publishing; and receiving support from ISSG for a non–study-related clinical or research effort that he oversees.

Author Contributions

Conception and design: DiGiorgio, Tsolinas, Haefeli, Talbott, Ferguson, Bresnahan, Beattie, Manley, Whetstone, Dhall. Acquisition of data: DiGiorgio, Tsolinas, Haefeli, Talbott, Ferguson, Bresnahan, Beattie, Manley, Whetstone, Dhall. Analysis and interpretation of data: DiGiorgio, Tsolinas, Dhall. Drafting the article: DiGiorgio, Tsolinas, Alazzeh, Dhall. Critically revising the article: DiGiorgio, Tsolinas, Alazzeh, Haefeli, Talbott, Ferguson, Bresnahan, Beattie, Manley, Whetstone, Dhall. Reviewed submitted version of manuscript: DiGiorgio, Tsolinas, Dhall. Approved the final version of the manuscript on behalf of all authors: DiGiorgio. Statistical analysis: DiGiorgio, Tsolinas, Dhall. Administrative/technical/material support: Tsolinas, Haefeli, Talbott, Ferguson, Bresnahan, Beattie, Manley, Whetstone, Mummaneni, Dhall. Study supervision: Manley, Mummaneni, Dhall.

Correspondence

Anthony M. DiGiorgio, Department of Neurosurgery, Louisiana State University Health Sciences Center, 2020 Gravier St., 7th Fl., New Orleans, LA 70112. email: adigi2@lsuhsc.edu.

Multivariate Analysis of MRI Biomarkers for Predicting Neurologic Impairment in Cervical Spinal Cord Injury

J. Haefeli, M.C. Mabray, W.D. Whetstone, S.S. Dhall, J.Z. Pan, P. Upadhyayula, G.T. Manley, J.C. Bresnahan, M.S. Beattie, A.R. Ferguson, and J.F. Talbott

ABSTRACT

BACKGROUND AND PURPOSE: Acute markers of spinal cord injury are essential for both diagnostic and prognostic purposes. The goal of this study was to assess the relationship between early MR imaging biomarkers after acute cervical spinal cord injury and to evaluate their predictive validity of neurologic impairment.

MATERIALS AND METHODS: We performed a retrospective cohort study of 95 patients with acute spinal cord injury and preoperative MR imaging within 24 hours of injury. The American Spinal Injury Association Impairment Scale was used as our primary outcome measure to define neurologic impairment. We assessed several MR imaging features of injury, including axial grade (Brain and Spinal Injury Center score), sagittal grade, length of injury, maximum canal compromise, and maximum spinal cord compression. Data-driven nonlinear principal component analysis was followed by correlation and optimal-scaled multiple variable regression to predict neurologic impairment.

RESULTS: Nonlinear principal component analysis identified 2 clusters of MR imaging variables related to 1) measures of intrinsic cord signal abnormality and 2) measures of extrinsic cord compression. Neurologic impairment was best accounted for by MR imaging measures of intrinsic cord signal abnormality, with axial grade representing the most accurate predictor of short-term impairment, even when correcting for surgical decompression and degree of cord compression.

CONCLUSIONS: This study demonstrates the utility of applying nonlinear principal component analysis for defining the relationship between MR imaging biomarkers in a complex clinical syndrome of cervical spinal cord injury. Of the assessed imaging biomarkers, the intrinsic measures of cord signal abnormality were most predictive of neurologic impairment in acute spinal cord injury, highlighting the value of axial T2 MR imaging.

ABBREVIATIONS: AIS = American Spinal Injury Association Impairment Scale; BASIC = Brain and Spinal Injury Center; MCC = maximum canal compromise; MSCC = maximum spinal cord compression; NL-PCA = nonlinear principal component analysis; PC = principal component; SCI = spinal cord injury

Early biomarkers of spinal cord injury (SCI) are essential during the acute phase of injury, a time when crucial management decisions are made and a period of great prognostic anxiety for patients and families.[1-3] As emerging experimental therapies translate to the clinic, early biomarkers will also be important for patient selection and monitoring in clinical trials. Multiple potential MR imaging biomarkers exist to evaluate acute SCI.[1,4-20] These measures primarily focus on the sagittal imaging plane, examining factors such as length of T2-hyperintense signal within the cord, whether abnormal signal is confined or spans multiple vertebral levels, presence of hemorrhage, and secondary markers of cord injury such as spinal cord compression and spinal canal compromise.[1,5-22] The internal structure of the spinal cord, with predominantly longitudinally oriented WM tracts, suggests that the axial injury extent and WM sparing should also be strong predictors of outcome. This concept has been demonstrated in preclinical studies and recently in human studies introduc-

Received August 1, 2016; accepted after revision October 4.

From the Departments of Neurological Surgery (J.H., S.S.D., P.U., G.T.M., J.C.B., M.S.B., A.R.F.), Radiology and Biomedical Imaging (M.C.M., J.F.T.), Emergency Medicine (W.D.W.), and Anesthesia and Perioperative Care (J.Z.P.), University of California San Francisco and Zuckerberg San Francisco General Hospital, San Francisco, California; Weill Institute for Neurosciences, Brain and Spinal Injury Center (J.H., W.D.W., S.S.D., J.Z.P., P.U., G.T.M., J.C.B., M.S.B., A.R.F., J.F.T.), San Francisco VA Medical Center (A.R.F.), San Francisco, California.

This work was supported by R01NS067092 (A.R.F.), R01NS088475 (A.R.F.), the Craig H. Neilsen Foundation (A.R.F., J.C.B.), Wings for Life Foundation (A.R.F.), and Department of Defense grant SC120259 (M.S.B., J.C.B.). M.C.M. was supported by a National Institutes of Health T32 Fellowship, 5T32EB001631-10. J.H. was supported by a Craig H. Neilsen Foundation fellowship (313739).

M.C.M. and J.H. contributed equally to this research and to the manuscript and are considered co–first authors.

Please address correspondence to Adam R. Ferguson, PhD, Department of Neurological Surgery, Zuckerberg San Francisco General Hospital, Building 1, Room 101, San Francisco, CA 94110; e-mail: adam.ferguson@ucsf.edu

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Indicates article with supplemental on-line tables.
Indicates article with supplemental on-line photo.

http://dx.doi.org/10.3174/ajnr.A5021

ing an axial scoring system known as the Brain and Spinal Injury Center (BASIC) score.[4,23-30] However, until now, it has been unclear how the axial grading relates to other imaging biomarkers of the sagittal plane and extrinsic compression measures.

The various MR imaging–based metrics have been shown to be reproducible, and all have some individual degree of predictive validity for clinical outcome.[1,4-20] Here, we evaluated the relationships of these MR imaging metrics to each other and to neurologic impairment. We applied a data-driven tool, nonlinear principal component analysis (NL-PCA), to understand the relationship between different MR imaging biomarkers and assess their ability to predict neurologic impairment. NL-PCA detects statistical patterns, incorporating multiple variables independent of their scale and decomposing them into a smaller set representing multidimensional clusters of variables (principal components [PCs]) that covary.[31,32] We then used nonlinear regression approaches to benchmark different MR imaging assessments against each other for predicting neurologic impairment at discharge. We hypothesized that MR imaging measures of acute cervical SCI would group together as a coherent multivariate PC ensemble and that distinct PCs (PC1, PC2, etc) would predict neurologic impairment. We intended 1) to provide insight into relationships between early MR imaging biomarkers after acute cervical SCI and 2) to provide an evaluation of the predictive validity of each individual measure of neurologic impairment.

MATERIALS AND METHODS

Study Cohort

This study was HIPAA and institutional review board compliant. We performed a retrospective cohort study of patients with acute blunt cervical SCI evaluated at a Level I trauma center (Zuckerberg San Francisco General Hospital) from 2005 to 2014. Inclusion criteria were 1) blunt acute cervical SCI, 2) age ≥18 years, 3) presurgical cervical spine MR imaging performed within 24 hours after injury, and 4) documented American Spinal Injury Association Impairment Scale (AIS) at both admission and discharge. Exclusion criteria were 1) penetrating SCI, 2) surgical decompression and/or fusion before MR imaging, 3) MR imaging that was too degraded by motion or other artifact such that images were nondiagnostic, and 4) preexisting surgical hardware. Of 212 patients initially identified, 95 patients met all inclusion and exclusion criteria and were included in the study. The data collected included sex and age, AIS at admission and discharge (as documented in the chart and performed by appropriately trained physiatrists and neurosurgeons), hours to MR imaging from time of injury, days to discharge, and whether surgical decompression of the cervical spine was performed before discharge. Fifty-two of the 95 patients included in this study were included in a cohort of patients as part of a previously published study.[4] This prior, smaller study involved initial development and interrater reliability testing of the BASIC score, whereas the current study tests multiple MR imaging grading schemes against each other, and against neurologic outcome, by using multivariate statistical analysis.

MR Imaging

All MR imaging examinations were acquired on the same 1.5T Genesis Signa scanner (GE Healthcare, Milwaukee, Wisconsin). We assessed sagittal T2 FSE, sagittal T1, and axial T2 FSE sequences performed as part of our routine imaging protocol, with these sequences not substantially changing over the study interval. Additional sequences performed as part of our trauma imaging protocol were not evaluated. Sequences were performed with the following parameters (presented as mean ± standard deviation from 10 randomly selected examinations): 1) for axial T2 FSE through the entire cervical spine: TR, 3798 ms ± 586 ms; TE, 102 ms ± 6 ms; section thickness, 3 ms; echo-train length, 17 ± 3.4; in-plane FOV, = 160 × 160 mm with a 512 × 512 matrix for nominal in-plane resolution of 0.31 mm^2; 2) for sagittal T2 FSE: TR, 3585 ms ± 563 ms; TE, 105 ms ± 5 ms; section thickness, 3 mm; echo-train length, 17.1 ± 3; in-plane FOV, 200 × 200 mm; and 3) for sagittal T1: TR, 528 ms ± 103 ms; TE, 16 ms ± 1.3 ms; section thickness, 3 mm; echo-train length, 2.6 ± 0.8; and in-plane FOV, 200 × 200 mm with a 512 × 512 matrix for nominal in-plane resolution of 0.39 mm^2.

Image Analysis

A neuroradiology fellow (M.C.M.) and attending physician (J.F.T.) performed consensus MR imaging ratings for all metrics while blinded to clinical outcome. The interrater reliability and BASIC axial MR imaging grading have been previously described as follows[4,30]: grade 0, no cord signal abnormality; grade 1, T2 hyperintensity confined to GM; grade 2, intramedullary T2 hyperintensity extends beyond expected gray matter margins to involve spinal white matter, but does not involve entire transverse extent of the spinal cord; grade 3, T2 hyperintensity involving GM and some but not all of WM; grade 4, T2 hyperintensity involving the entire axial plane of the spinal cord; grade 5, grade 3 injury with the addition of foci of T2 hypointensity consistent with hemorrhage. Sagittal grading was assigned as previously described: grade 1, no spinal cord signal abnormality; grade 2, single-level T2 hyperintensity; grade 3, >1 vertebral level T2 signal hyperintensity; grade 4, T2 signal hyperintensity with areas of hypointensity representing hemorrhage.[1,19] The greatest length (mm) of injury on sagittal T2 was measured as described in the National Institutes of Health/National Institute of Neurologic Disorders and Stroke SCI common data elements version 1.0.[3] Maximum canal compromise (MCC) and maximum spinal cord compression (MSCC) assessed midsagittal images by dividing the anteroposterior diameter of the canal (on sagittal T1 for MCC) and the anteroposterior diameter of spinal cord (on sagittal T2 for MSCC) by the average of the canal or spinal cord above and below as previously described.[8,15,16,22]

Multidimensional Analysis Workflow and Statistical Analysis

NL-PCA assessed the relationship among MR imaging measures by incorporating pattern detection with optimal-scaling transformations to accommodate nonparametric, ordinal, and nonlinear relationships that are common in clinical assessment tools such as MR imaging scoring by a radiologist.[33,34] Established decision rules defined the final dimensionality: Kaiser rule criterion of eigenvalue >1 and Cattell rule (ie, scree plot).[33-36] Validity of MR imaging and PC scores for predicting AIS at discharge involved linear mixed model, Spearman rank correlation, and an optimal-scaled regression.

Receiver operating characteristic curves assessed sensitivity and specificity of MR imaging measures for predicting AIS at

discharge by using a sliding scale (ie, AIS A versus B, C, D, E; AIS A, B versus C, D, E; AIS A, B, C versus D, E; and AIS A, B, C, D versus E), resulting in 4 separate receiver operating characteristic curves. In addition, we completed a supplementary analysis where we compared adjacent groups. Because of the low number of patients in the AIS B subgroup ($n = 3$), AIS A and B were grouped together as a motor complete group. We compared the areas under the curve of the different MR imaging biomarkers.

In a next step, we used discriminant function analysis to assess within the BASIC measure the optimal combination of scores to discriminate the different AIS groups. BASIC score was recoded as: 1) a simple lesion/no lesion score (BASIC 0 = no lesion, and BASIC 1–4 = any lesion) and 2) into a 3-point scale merging BASIC score subcategories 1–3 into 1 category. All MR imaging variables and the 2 recoded BASIC score variables were fed into a discriminant function analysis test for discrimination of AIS at discharge. Statistical significance for all tests was set at $\alpha = .05$. All statistical analyses were performed in SPSS v.23 (IBM, Armonk, New York). Syndromic plots for the PC loadings were generated in custom-designed software in R (http://www.r-project.org/).[37]

Table 1: Patient characteristics[a]

Age	57.91 ± 18.15
Sex (M, F)	67, 28
AIS at admission	A = 26, B = 9, C = 18, D = 42
AIS at discharge	A = 17, B = 3, C = 15, D = 41, E = 19
Time to MRI (hours)	6.97 ± 5.15
Time to discharge (days)	25.15 ± 35.31
Surgical decompression	Yes = 63, No = 32

[a] Values expressed as *N* or mean ± SD.

Table 2: MRI scoring schemes

BASIC	Ordinal	0–4: 0 = normal; 1 = GM only; 2 = some WM; 3 = all WM in plane; 4 = with hemorrhage
Sagittal grade	Ordinal	1–4: 1 = normal; 2 = less than a VB; 3 = longer than 1 VB; 4 = with hemorrhage
Longitudinal extent of T2 signal abnormality	Numeric	[mm]
MCC	Numeric	MCC % = $1 - \{D_i/[(D_a + D_b)/2]\} \times 100\%$; D = canal width[a]
MSCC	Numeric	MSCC % = $1 - \{d_i/[(d_a + d_b)/2]\} \times 100\%$; d = spinal cord width[a]

Note:—VB indicates vertebral body.
[a] See Fig 1 for further description.

RESULTS

Patient characteristics are listed in Table 1. MR imaging measurements are outlined in Table 2 and Fig 1. The relationships between the BASIC score and AIS at discharge are listed in Table 3. NL-PCA demonstrated all imaging parameters loaded highly on PC1. PC2 discriminated MR imaging measures, with only MSCC and MCC showing high loadings (On-line Fig 1*A*). Statistical decision rules pruned the initial 5-dimensional NL-PCA solution to 2 dimensions (On-line Fig 1*B*). The optimal-scaled transformation matrix revealed a high correlation between the lesion length, sagittal grade, and the BASIC score and, to a lesser extent, between the compression variables (MSCC and MCC) (Fig 2*A*). The loading patterns of the 2-dimensional NL-PCA solution are displayed in Fig 2*B*. PC1–2 accounted for 88.6% of the total variance in the dataset (PC1, 58.6%; PC2, 30%). All imaging variables loaded highly on PC1. Variance explained by PC1 represents convergence across all MR imaging variables. In contrast, PC2 mainly captures compression variables MSCC and MCC, representing divergence of the MR imaging variables of intrinsic cord signal abnormality.

In Fig 2*C*, individual PC scores are projected into PC1 and PC2 space, with each patient color-coded by AIS change and by AIS grade at discharge. Patients with higher scores on the PC1 axes have worse AIS at discharge. Confirming this,

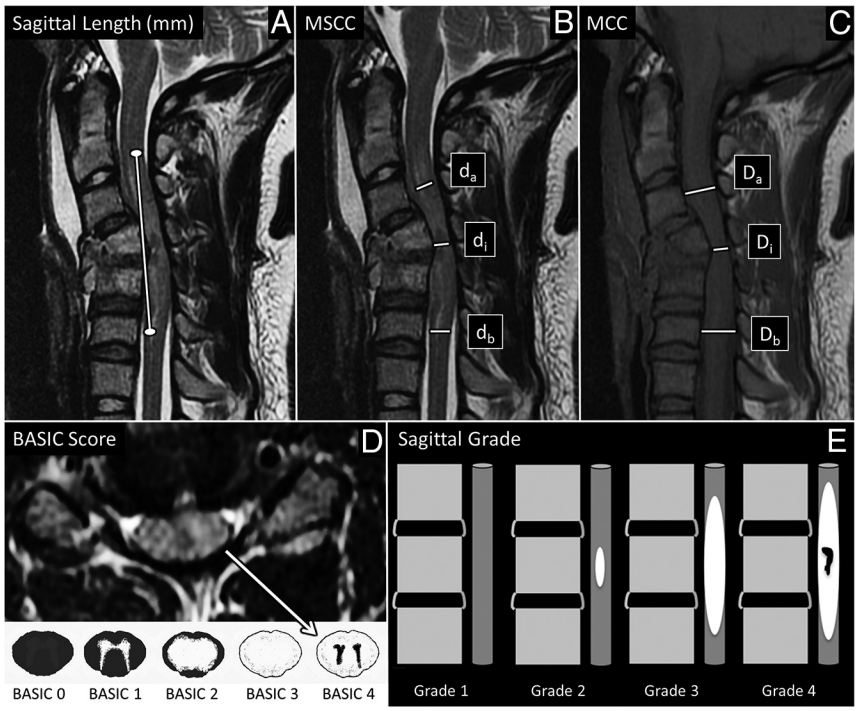

FIG 1. MR imaging-based metrics. *A* and *B*, Sagittal T2-weighted MR imagings of the cervical spine of patients with acute SCI were used to measure the length of T2 signal hyperintensity in mm (*A*, *white line*) and to calculate MSCC (*B*, $1 - \{d_i/[(d_a + d_b)/2]\} \times 100\%$). d_i indicates distance of the spinal cord at the injury site; d_b, one segment below the injury site; d_a, one segment above the injury site. *C*, Sagittal T1-weighted image of the cervical spine demonstrating how we used this sequence to measure MCC ($1 - \{D_i/[(D_a + D_b)/2]\} \times 100\%$). D_i indicates distance of the spinal canal at the injury site; D_b, one segment below the injury site; D_a, one segment above the injury site. *D*, The axial T2-weighted MR imaging of the cervical spine at the level of the epicenter of injury was used to define the BASIC score. Areas of macroscopic T2-hypointense hemorrhage are surrounded by hyperintense edema with no normal cord signal, consistent with BASIC grade 4. BASIC axial grade cartoons are depicted in the *lower panel*. *E*, Shows cartoons of the sagittal grading system. Sag indicates sagittal.

a linear mixed model revealed that PC1, but not PC2, significantly predicted AIS at discharge (PC1: $F = 33.79$, $P < .001$; PC2: $F = 2.11$, $P = .086$).

To compare predictive validity of PC1 and PC2 versus univariate MR imaging measures, we applied univariate nonparametric Spearman rank correlations for prediction of AIS at discharge (Table 4 and Fig 3). Based on Spearman rank correlation, variables of intrinsic cord signal abnormality (lesion length, sagittal grade, BASIC score) and both PC1 and PC2 predicted AIS at discharge. Neither MSCC nor MCC significantly correlated with AIS at discharge. Lesion length ($\rho = -0.66$), sagittal grade ($\rho = -0.70$), BASIC score ($\rho = -0.85$), and PC1 ($\rho = -0.69$) all negatively correlated with AIS at discharge, whereas PC2 showed a weak positive correlation with AIS at discharge ($\rho = 0.22$).

We used optimal-scaled regression to benchmark the predictive validity of MR imaging measures against each other. An advantage of the optimal-scaled regression is that it takes into account different analysis levels (ordinal versus continuous) in a single model. PC scores were not included in this analysis because of multicollinearity. BASIC was the only significant predictor of AIS at discharge ($P < .01$).

We next benchmarked how individual MR imaging measures perform in predicting AIS at discharge compared with AIS at admission. Not surprisingly, AIS at admission showed a strong positive correlation with AIS at discharge by Spearman rank correlation ($\rho = 0.82$, $P < .01$). Optimal-scaling regression revealed that BASIC score and AIS at admission were the only significant predictors of AIS at discharge (both $P < .01$) (On-line Table 1).

We were concerned that BASIC prediction of AIS at discharge may be confounded by the decision to perform surgical decompression, which could also influence outcome. To test this, we performed 2 additional waves of analysis. First, we tested whether BASIC score significantly predicted the decision to perform surgical decompression by using a generalized linear model. BASIC score significantly predicted surgical decompression decision-making (Wald $\chi^2 = 9.00$, $P = .003$). To test whether this confounded BASIC's predictive validity for AIS at discharge, we reran the generalized linear model with an interaction term, testing whether BASIC and surgical decompression were statistically entangled. This analysis maintained the significant predictive main effect of BASIC on AIS (Wald $\chi^2 = 34.92$, $P < .001$). Furthermore, undergoing decompression surgery was not a significant predictor of AIS at discharge (Wald $\chi^2 = 0.17$, $P = .68$), nor was there a significant interaction between BASIC and decompression surgery (Wald $\chi^2 = 1.58$, $P = .66$). Similarly, we wanted to assess if BASIC significantly predicts AIS at discharge after correcting for MSCC. Using the same analysis tools, the predictive validity of BASIC was maintained ($F = 30.69$, $P < .001$), and there was no interaction effect between AIS at discharge and MSCC ($F = 0.79$, $P = .53$).

The sensitivity and specificity (receiver operating characteristic and area under the curve) of the MR imaging

Table 3: BASIC score in relation to AIS at discharge[a]

	AIS A	AIS B	AIS C	AIS D	AIS E	Total Patients
BASIC 0				1 (7.7)	12 (92.3)	13
BASIC 1				12 (70.6)	5 (29.4)	17
BASIC 2		1 (2.6)	10 (25.6)	26 (66.7)	2 (5.1)	39
BASIC 3	7 (43.8)	2 (12.5)	5 (31.3)	2 (12.5)		16
BASIC 4	10 (100)					10

[a] Data presented as no. of patients (%).

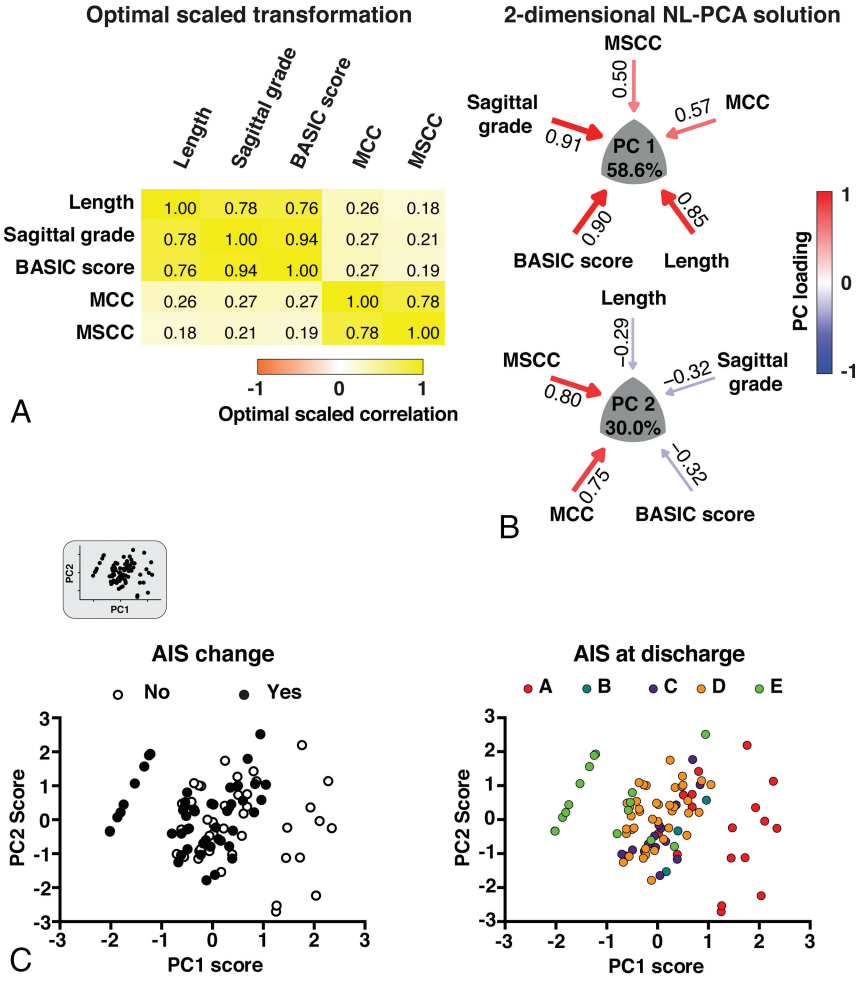

FIG 2. Results of the 2-dimensional NL-PCA. *A*, Heat map of the optimal-scaled transformation matrix of all MR imaging measures included in the NL-PCA. The matrix indicates all bivariate cross-correlations: *yellow* indicates a positive relationship and *orange* indicates a negative relationship. *B*, 2-dimensional NL-PCA solution. PCs reflect the clustered variance shared by the MR imaging measures and are represented by a *convex triangle*. The *arrow gauge* and the intensity of the color (*red* indicates a positive relationship and *blue* indicates a negative relationship) show the magnitude (ie, loading weights) of the correlation between each MR imaging measure and the PC. *C*, Bi-plots of individual patients ($n = 95$) in the 2-dimensional space described by PC1 and PC2. In the *top left corner*, the extracted bi-plot is displayed. In the *left graph*, the same bi-plot is color-coded by AIS change (ie, AIS change from admission to discharge) and is color-coded in the *right graph* by AIS at discharge. PCA indicates principal component analysis.

Table 4: Predicting AIS at discharge—Spearman rank correlation and optimal scaling regression results

	Spearman Correlation			Optimal Scaling Regression			
	ρ	ρ^2	*P* Value	Zero-Order	Partial	Part	*P* Value
Length	−0.66	0.44	<.01	−0.65	−0.11	−0.05	.50
Sagittal grade	−0.70	0.49	<.01	−0.69	0.36	0.18	.10
BASIC score	−0.85	0.72	<.01	−0.87	−0.75	−0.50	<.01
MCC	−0.20	0.04	.05	−0.24	0.02	0.01	.90
MSCC	−0.14	0.02	.18	−0.20	−0.08	−0.04	.62
PC1	−0.69	0.48	<.01				
PC2	0.22	0.05	.03				

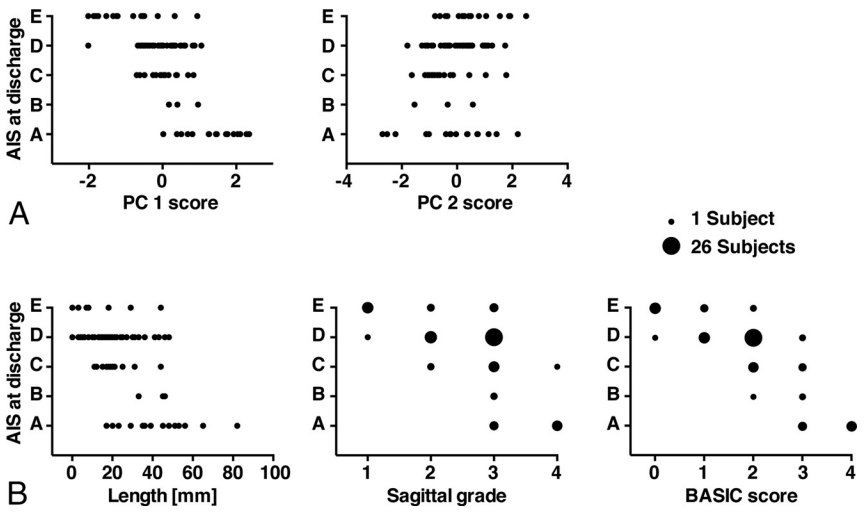

FIG 3. Multivariate (PCs) and univariate prediction of AIS at discharge. *A*, PC1 was negatively correlated with AIS at discharge, and PC2 showed a weak positive correlation. *B*, The length of the lesion, the sagittal grade, and the BASIC score showed a negative correlation with AIS at discharge. Note that because of the ordinal scale of the BASIC score and the sagittal grade, some subjects coincide on the same value. The number of subjects within each sphere is represented by the size of the spheres. Only scatterplots of the statistically significant correlations between the MR imaging measures and AIS at discharge are displayed.

measures in predicting AIS at discharge are shown in Fig 4 (AIS sliding scale). Supporting previous analysis, the length, sagittal grade, and BASIC score predicted AIS at discharge, with their areas under the curve statistically superior to random guessing (Table 5). BASIC consistently had the highest area under the curve in comparison with the other MR imaging measures. In a supplementary analysis, we tested how well the MR imaging measures can discern adjacent AIS categories. The results are shown in On-line Table 2. Similar to the sliding scale results, BASIC consistently had the highest area under the curve for distinguishing both severe and mild AIS categories in comparison with the other MR imaging measures.

Finally, to assess discriminative value score subcategories, we applied a linear discriminant function analysis. This supervised pattern detection approach discovers the optimal combination of scores to discriminate the different AIS groups. The full BASIC score had the largest absolute correlation with the canonical discriminant function for AIS, suggesting that the full 5-point BASIC score performs better than truncated scoring schemes (0.962). The full BASIC score outperformed both the simple dichotomous score (lesion versus no lesion, with BASIC 0 = no lesion and BASIC 1–4 = any lesion; 0.388) and a 3-point scale merging BASIC score subcategories 1–3 into 1 category (BASIC 0 = no lesion, BASIC 1–3 = nonhemorrhagic lesion, BASIC 4 = hemorrhagic lesion; 0.639). A second discriminant function analysis included only patients with a BASIC score of 1–3 (ie, those patients with nonhemorrhagic intramedullary T2 signal abnormality) to define the prognostic value of BASIC in this specific subpopulation. BASIC had the largest absolute correlation with the discriminative function (0.991), followed by the length of the lesion (0.416).

DISCUSSION

We applied data-driven multivariate analytic techniques to evaluate how multiple MR imaging–derived metrics relate to each other and to short-term impairment when applied to a group of 95 patients with acute blunt cervical SCI. We identified 2 principal components (PC1 and PC2) that explained 88.6% of the total variance in the dataset. Measures of intrinsic spinal cord signal abnormality had the highest positive loading on PC1, whereas measures of extrinsic cord compression had more modest positive loading. Both the BASIC score and sagittal grade had greater correlation with outcome than PC1, whereas BASIC score was the only univariate MR imaging measure to correlate with outcome when correcting for differences in data measurement scales. The present results support the prognostic relevance of the BASIC score compared with other MR imaging measures of SCI.

Although all imaging variables loaded positively on PC1, PC2 was more discriminatory in nature, segregating structural measures of compression from variables reflecting intrinsic cord signal abnormality. PC2 had a weakly positive correlation with AIS ($\rho = 0.22$, $P = .03$), whereas measures of extrinsic compression had no significant correlation with outcome. These findings demonstrate the discriminant validity of NL-PCA and highlight the split between MR imaging measures of intrinsic cord signal abnormality and structural measures of compression.[30] Structural measures of compression thus have a complex relationship with outcome. The present data do not necessarily conflict with prior work examining the predictive validity of MSCC in acute SCI.[8,15,16,21,22] Miyanji and colleagues[8] showed that MSCC was a key predictor of neurologic recovery after traumatic SCI. In that study, outcome for patients with SCI was dichotomized into complete and incomplete categories, whereas we have used the more granular 5-point AIS grading scale. In addition, after correcting for baseline neurologic status, only intrinsic measures of SCI significantly correlated with neurologic recovery, findings consistent with the present results.[8]

Receiver operating characteristic analysis confirmed that of the imaging variables examined, the BASIC score was the most accurate for predicting short-term impairment. We were con-

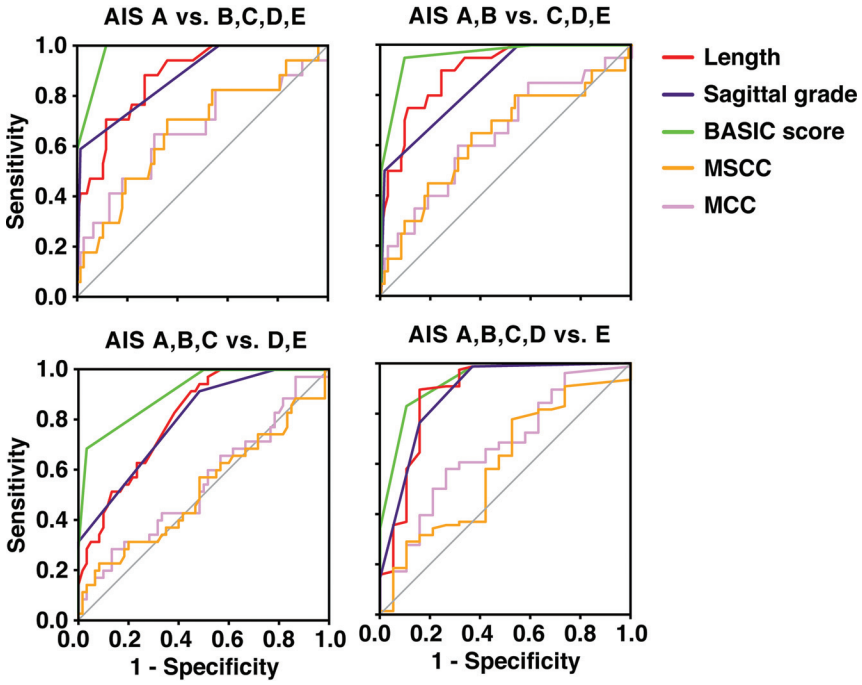

FIG 4. Receiver operating characteristic curves for the different MR imaging measures. The curves show the sensitivity and specificity of the different measures to predict AIS at discharge. AIS at discharge was dichotomized by using a sliding scale, resulting in 4 separate receiver operating characteristic curves (AIS A versus B, C, D, E; AIS A, B versus C, D, E; AIS A, B, C versus D, E; and AIS A, B, C, D versus E). The *diagonal gray line* represents a reference line that corresponds to random guessing. The further the receiver operating characteristic curves are located to the *top left corner*, the higher is the sensitivity and specificity of the measure in predicting the dichotomized AIS at discharge.

Table 5: Receiver operating characteristic analysis results

	AUC	*P* Value	95% CI
AIS A vs. B, C, D, E			
Length	0.88	<.01	0.80–0.96
Sagittal grade	0.88	<.01	0.79–0.97
BASIC score	0.98	<.01	0.95–1.00
MCC	0.66	.039	0.50–0.82
MSCC	0.66	.036	0.51–0.81
AIS A, B vs. C, D, E			
Length	0.90	<.01	0.83–0.97
Sagittal grade	0.86	<.01	0.77–0.94
BASIC score	0.96	<.01	0.92–1.00
MCC	0.65	.05	0.50–0.79
MSCC	0.64	.06	0.49–0.79
AIS A, B, C vs. D, E			
Length	0.81	<.01	0.72–0.89
Sagittal grade	0.80	<.01	0.71–0.89
BASIC score	0.91	<.01	0.85–0.97
MCC	0.55	.44	0.43–0.67
MSCC	0.52	.71	0.40–0.65
AIS A, B, C, D vs. E			
Length	0.88	<.01	0.77–0.99
Sagittal grade	0.88	<.01	0.79–0.98
BASIC score	0.93	<.01	0.86–0.99
MCC	0.66	.03	0.52–0.80
MSCC	0.59	.21	0.45–0.74

Note:—AUC indicates area under the curve.

cerned that other factors may confound the prognostic validity of the BASIC score. For example, the decision to perform surgical decompression may be influenced by the presence and pattern of signal abnormality in the spinal cord, which could influence outcome.[38-40] In addition, the extent of spinal cord compression with associated cord deformation may potentially confound BASIC grading. Our analysis confirms that the predictive validity of the BASIC score was maintained after correcting for potential interactions from surgical decompression and spinal cord compression.

Prior studies suggest MR imaging is most accurate at predicting outcomes when patients have evidence for very mild (normal cord signal) or very severe (intramedullary hemorrhage) injury.[1,6,7,10,13,14,20] In contrast, tremendous variability in clinical outcomes has been described in the setting of intermediate degrees of injury.[1] To specifically evaluate MR imaging measures and outcomes in this subgroup of patients from our cohort, we applied discriminant function analysis to patients with a BASIC score of 1–3 (patients with nonhemorrhagic intramedullary T2 signal hyperintensity; $n = 72$). Even in this subpopulation, the BASIC score had a very high absolute correlation with the discriminant function (0.991), followed by the length of the lesion (0.416). Therefore, the prognostic capabilities of the BASIC score are not simply attributable to the ease of prognosis at the ends of the injury severity spectrum.

Limitations of our study primarily relate to the retrospective, single-institution study design. We are actively pursuing this subject further in a prospective fashion with longer clinical follow-up at multiple time points and more detailed outcome measures. Our technique was designed to look at the relationships of the various imaging metrics to each other and to clinical outcome (AIS at discharge). Although we believe that the current study is adequate for investigating these relationships, we realize that there are changes in neurologic impairment expected over a longer time course. In addition, in a future prospective study, more detailed outcome measures need to be included to more comprehensively capture neurologic function.

CONCLUSIONS

This study demonstrates the utility of applying NL-PCA for defining the relationship between MR imaging biomarkers in a complex clinical syndrome of cervical SCI. Independent, prospective studies are needed to validate our conclusion that intrinsic measures of spinal cord pathology on acute MR imaging, particularly the BASIC score, best predict neurologic impairment in acute SCI compared with measures of extrinsic compression. This analytic pipeline is suited for future patient-level investigation and is amenable to inclusion of emerging potential biomarkers. Multidimensional approaches may also be useful for future prospective validation of imaging metrics

derived from advanced quantitative techniques such as DTI, which are under active investigation for spinal cord pathology.[26,41-43]

Disclosures: Jenny Haefeli—*RELATED*: *Grant*: Craig H. Neilsen Foundation, *Comments*: Craig H. Neilsen postdoctoral scholar*; *UNRELATED*: *Grants/Grants Pending*: Craig H. Neilsen Foundation, *Comments*: Craig H. Neilsen postdoctoral scholar. William Whetstone—*RELATED*: *Grant*: Department of Defense, *Comments*: grant 2013–2016.* Sanjay Dhall—*UNRELATED*: *Other*: DePuy Spine, Globus Spine, *Comments*: speaking honoraria. Pavan Upadhyayula—*RELATED*: *Grant*: National Institutes of Health.* Jacqueline Bresnahan—*RELATED*: *Grant*: Department of Defense*; *Support for Travel to Meetings for the Study or Other Purposes*: Department of Defense*; *UNRELATED*: *Grants/Grants Pending*: National Institutes of Health, Department of Defense, Craig H. Neilsen Foundation.* Michael Beattie—*RELATED*: *Grant*: Department of Defense Congressionally Directed Medical Research Programs - Spinal Cord Injury Research Program, *Comments*: grant SC120259, principal investigator.* Adam Ferguson—*RELATED*: *Grant*: National Institutes of Health/National Institute of Neurologic Disorders and Stroke, Wings for Life Foundation, Craig H. Neilsen Foundation, *Comments*: principal investigator on multiple grants cited in the paper that supported the work*; *UNRELATED*: *Grants/Grants Pending*: National Institutes of Health, Department of Defense, Veterans Affairs, Craig H. Neilsen Foundation, Wings for Life Foundation, *Comments*: principal investigator or co-investigator on many grants unrelated to the reported work.* Jason Talbott—*UNRELATED*: *Other*: StemCells, Inc, *Comments*: member of data monitoring committee for clinical trial which is now ended. *Money paid to the institution.

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JOURNAL OF NEUROTRAUMA 33:954–962 (May 15, 2016)

DOI: 10.1089/neu.2015.4093

Multidimensional Analysis of Magnetic Resonance Imaging Predicts Early Impairment in Thoracic and Thoracolumbar Spinal Cord Injury

Marc C. Mabray,[1] Jason F. Talbott,[1,5] William D. Whetstone,[2,5] Sanjay S. Dhall,[3,5] David B. Phillips,[3,5] Jonathan Z. Pan,[4,5] Geoffrey T. Manley,[3,5] Jacqueline C. Bresnahan,[3,5] Michael S. Beattie,[3,5] Jenny Haefeli,[3,5] and Adam R. Ferguson[3,5,6]

Abstract

Literature examining magnetic resonance imaging (MRI) in acute spinal cord injury (SCI) has focused on cervical SCI. Reproducible systems have been developed for MRI-based grading; however, it is unclear how they apply to thoracic SCI. Our hypothesis is that MRI measures will group as coherent multivariate principal component (PC) ensembles, and that distinct PCs and individual variables will show discriminant validity for predicting early impairment in thoracic SCI. We undertook a retrospective cohort study of 25 patients with acute thoracic SCI who underwent MRI on admission and had American Spinal Injury Association Impairment Scale (AIS) assessment at hospital discharge. Imaging variables of axial grade, sagittal grade, length of injury, thoracolumbar injury classification system (TLICS), maximum canal compromise (MCC), and maximum spinal cord compression (MSCC) were collected. We performed an analytical workflow to detect multivariate PC patterns followed by explicit hypothesis testing to predict AIS at discharge. All imaging variables loaded positively on PC1 (64.3% of variance), which was highly related to AIS at discharge. MCC, MSCC, and TLICS also loaded positively on PC2 (22.7% of variance), while variables concerning cord signal abnormality loaded negatively on PC2. PC2 was highly related to the patient undergoing surgical decompression. Variables of signal abnormality were all negatively correlated with AIS at discharge with the highest level of correlation for axial grade as assessed with the Brain and Spinal Injury Center (BASIC) score. A multiple variable model identified BASIC as the only statistically significant predictor of AIS at discharge, signifying that BASIC best captured the variance in AIS within our study population. Our study provides evidence of convergent validity, construct validity, and clinical predictive validity for the sampled MRI measures of SCI when applied in acute thoracic and thoracolumbar SCI.

Key words: BASIC; MRI; spinal cord injury; thoracic; T2 hyperintensity; TLICS

Introduction

Acute traumatic spinal cord injury (SCI) involving the thoracic and thoracolumbar spinal cord is considerably less common than cervical SCI with approximately 10% of SCI involving the thoracic spine and another 6% involving the cervicothoracic or thoracolumbar junctions.[1] Most of the literature examining MRI findings in acute traumatic SCI have focused on the more common injury to the cervical spinal cord with relatively little attention given to acute SCI caudal to the cervical level.[2–23] Anatomic and functional distinctions are significant between the cervical and more caudal spinal cord segments, suggesting imaging evaluation may, in fact, be level specific.[24,25]

Since the widespread adoption of magnetic resonance imaging (MRI) in evaluating the spinal cord in the acute setting, there have been numerous studies examining the prognostic value of MRI in acute cervical spinal cord trauma.[2–5,7,9,11–23,26,27] The majority of these studies have focused on the longitudinal extent of T2 signal abnormality in the sagittal plane or secondary markers of SCI, such as canal and spinal cord compression in the cervical spine.[2,3,5,7,9,11–23,26–29] The internal architecture of the spinal cord, however, including the predominant longitudinal orientation of functionally important ascending and descending white matter tracts, would suggest that the transverse extent of injury should be a strong predictor of clinical outcome; this hypothesis has been corroborated by pre-clinical and, more recently, human studies.[4,8,30–35]

Departments of [1]Radiology and Biomedical Imaging, [2]Emergency Medicine, [3]Neurological Surgery, and [4]Anesthesia and Perioperative Care, University of California San Francisco and San Francisco General Hospital, San Francisco, California.
[5]Brain and Spinal Injury Center, San Francisco General Hospital, San Francisco, California.
[6]San Francisco Veteran's Affairs Medical Center, San Francisco, California.

A number of reproducible systems have been developed for MRI-based grading in acute SCI. The most recent addition is a grading system for the axial plane, termed the Brain and Spinal Injury Center (BASIC) score.[4] The BASIC score can be used in combination with other measures, including a commonly used sagittal grading system, the longitudinal extent of T2 signal abnormality, maximum canal compromise (MCC), maximum spinal cord compression (MSCC), and the thoracolumbar injury classification system (TLICS). With the exception of TLICS, these injury classification systems were initially developed for the more common cervical SCI but could have prognostic value throughout the spinal axis. In this study, we aim to evaluate the application of the various MRI grading systems in the setting of acute thoracic SCI.

We applied multidimensional data-driven analytics to the full set of imaging classifications to assess validity of these MRI metrics for thoracic SCI. Our hypothesis is that the BASIC score and the other MRI measures of SCI will group together as coherent multivariate principal component (PC) ensembles, and that distinct PCs (PC1, PC2, etc.) will show discriminant validity for predicting distinct impairment patterns in thoracic and thoracolumbar SCI at the time of patient discharge.

To test this hypothesis, we performed an analytical workflow of data-driven discovery to detect multivariate PC patterns followed by explicit hypothesis testing of whether the PCs and the individual MRI measures predict neurologic impairment at discharge. Multidimensional data-driven analytics (i.e., nonlinear PC analysis [NLPCA]) were applied to explore the multivariate clustering among various MRI measures to determine their convergent validity and discriminant validity.

Linear mixed modeling (LMM) was then applied to assess the relationship of these ensemble MRI measures with the degree of neurologic impairment measured by the American Spinal Injury Association (ASIA) Impairment Scale (AIS) at hospital discharge.[36,37] The results provide evidence of face validity, convergent validity, discriminant validity, construct validity, and clinical predictive validity for multiple MRI measures when applied in acute thoracic SCI.

Methods

Study cohort

We performed an Institutional Review Board and Health Insurance Portability and Accountability Act compliant retrospective cohort study evaluating patients who presented to a Level I trauma center between 2005 and 2012 with acute thoracic or thoracolumbar SCI. Patients were identified using a Department of Neurological Surgery database compiled of patients with a principal diagnosis of SCI (International Classification of Diseases codes 952–957).

Inclusion criteria were: (1) age ≥18 years, (2) thoracic and/or lumbar spine MRI including at minimum sagittal and axial T2 imaging, and (3) documented clinical assessments including AIS at admission and discharge. Exclusion criteria were (1) surgical decompression and/or fusion before MRI, (2) MRI that was too degraded by motion or other artifact such that images were nondiagnostic as assessed by an attending neuroradiologist, (3) cervical spinal cord injury, and (4) injuries primarily involving the conus medullaris or cauda equina nerve roots, (5) pre-existing hardware.

Twenty-five patients met inclusion and exclusion criteria. Clinical data collected included patient age, sex, AIS grade at discharge, time to MRI, time to discharge, mechanism, and whether surgical decompression was performed before hospital discharge (Table 1). All patients in the study cohort had a principal diagnosis of SCI and underwent our institutional SCI treatment protocol. The five patients classified as AIS grade E on formal admission examination had documented symptoms of truncal/lower extremity sensory deficits and/or had documentation of motor weakness in the field. These deficits had resolved AT neurological examination on admission and therefore qualify as AIS grade E.

MRI

All MRI were acquired on a 1.5 Tesla GE Genesis Signa HDxt scanner, software version 15 (GE Healthcare, Milwaukee, WI). Routine trauma protocol thoracic spine MRIs were performed including at minimum sagittal T1 and T2 fast spin echo (FSE) sequences and axial T2 FSE sequences. For sagittal T1 imaging, the following parameters were used: slice thickness = 3 mm; time to repetition (TR) = between 520 msec and 630 msec; time to echo (TE) = between 9 msec and 15 msec; echo train length (ETL) = 3; field-of-view (FOV) = 30 cm^2; acquisition matrix = 512 × 512. For sagittal T2: slice thickness, FOV, and matrix size were as above with TR between 3100 msec and 4000 msec and TE between 105 msec and 120 msec; ETL was between 19 and 21. For axial T2 imaging, slice thickness was 4 mm, TR between 4000 and 4800 msec, TE between 102 and 120 msec, ETL = 25, FOV = 18 cm, and acquisition matrix size = 512 × 512. Additional sequences were performed but not evaluated for the purposes of this study.

Image analysis

A board certified neuroradiologist and a neuroradiology trainee performed independent imaging ratings (Table 2), blinded to clinical outcomes, on retrospectively evaluated imaging sequences (Fig. 1). Any disagreements in categorization were discussed with ultimate deferral to the more experienced reader. The level of injury was defined as the epicenter of largest anterior to posterior extent of

Table 1. Patient Characteristics*

Characteristics	
Age (years)	38.32 ± 15.74
Sex	17 male: 8 female
Injury type	Blunt = 21, penetrating = 4
AIS at admission	A = 11, B = 2, C = 1, D = 6, E = 5
AIS at discharge	A = 9, B = 0, C = 2, D = 5, E = 9
Time to MRI (hours)	14.68 ± 18.56
Time to discharge (days)	20.96 ± 21.48
Surgical decompression before discharge	Yes = 16, No = 9
Mechanism of injury	10 fall from height, 5 motor vehicle collision, 3 crush injuries by large falling objects, 2 gunshot wounds, 2 stab wounds, 1 motorcycle collision
Vertebral body level of epicenter of injury by imaging	1 T2, 1 T3, 1 T4, 3 T6, 2 T7, 3 T8, 2 T9, 1 T11, 7 T12, 3 T1, 1 without detectable injury
BASIC score	1.88 ± 1.67
Sagittal grade	2.32 ± 1.22
Longitudinal extent of injury (mm)	23.52 ± 26.56
TLICS Score	5.16 ± 2.78
MCC (%)	23.38 ± 27.36
MSCC (%)	18.67 ± 24.02

*Results are expressed as N or mean ± standard deviation.

AIS, American Spinal Injury Association (ASIA) Impairment Scale; MRI, magnetic resonance imaging; BASIC, Brain and Spinal Injury Center; TLICS, thoracolumbar injury classification system; MCC, maximum canal compromise; MSCC, maximum spinal cord compression.

Table 2. Magnetic Resonance Imaging Scoring Schemes

Brain and Spinal Injury Center grading system	Ordinal	0–4; 0 = normal, 1 = gray matter only, 2 = some WM, 3 = all WM in plane, 4 = with hemorrhage.
Sagittal grade	Ordinal	1–4; 1 = normal, 2 = less than a vertebral body (VB), 3 = longer than one VB, 4 = with hemorrhage
Longitudinal extent of T2 signal abnormality	Numerical	(mm)
Thoracolumbar injury classification system	Ordinal	Rates: morphology (1–4), neurologic status (0–3), and integrity of the posterior ligamentous complex (0–3)
Maximum canal compromise (MCC)	Numerical	MCC (%) = 1−[Dx/(Da+Db)/2] × 100%; D: canal width
Maximum spinal cord compression (MSCC)	Numerical	MSCC (%) = 1−[dx/(da+db)/2] × 100%; d: spinal cord width

cord signal abnormality on sagittal imaging or as the level of bony injury/canal compromise if there was no cord signal abnormality.

BASIC grading was performed as has been described previously (Fig. 1D) by reviewing the axial images at the epicenter of the injury: briefly, grade 0 injury represented normal spinal cord T2 signal, grade 1 injury represented T2 hyperintensity approximately confined to expected location of spinal gray matter, grade 2 injury represented T2 hyperintensity extending beyond the expected margins of central gray matter and obscuring gray-white margins but not involving the entire transverse extent of the spinal cord (a peripheral rim of normal appearing white matter was identified), grade 3 injury represented T2 hyperintensity involving the entire transverse extent of the spinal cord without any residual normal appearing white matter, and grade 4 injury represented grade 3 injury with superimposed discrete foci of intramedullary T2 hypointensity attributed to the presence of macroscopic intramedullary hemorrhage.[4]

All BASIC scoring was based on a single axial image from the injury epicenter that was determined to have the most severe grade among all axial slices. Sagittal grade was assigned as follows (Fig. 1E): grade 1 represented normal spinal cord signal; grade 2 represented T2 hyperintense intramedullary signal with longitudinal extent confined to a single vertebral level; grade 3 represented >1 vertebral level edema; and grade 4 represented mixed hemorrhage and edema.[2,3]

We also measured the greatest longitudinal extent of injury on sagittal T2 images in mm as described in the SCI common data elements (CDE) version 1.0 (Fig. 1A). MCC and MSCC were also both measured on midsagittal images as described previously, by dividing the anterior-posterior (AP) diameter of the canal (for MCC) and the AP diameter of spinal cord (for MSCC) by the average of the canal or spinal cord above and below as described in the literature with MCC measured on T1 and MSCC measured on T2 (Fig. 1B,C).[11,19,27,29,38] TLICS was assigned as described in the literature after reviewing any necessary computed tomography (CT) imaging and the clinical chart.[39–41]

Multidimensional analytical workflow and statistical analysis

All statistical analyses were performed in SPSS v. 22 (SPSS Inc.; Chicago, IL). To assess the relationship between the different MRI measures, we used a NL-PCA in the general workflow depicted in

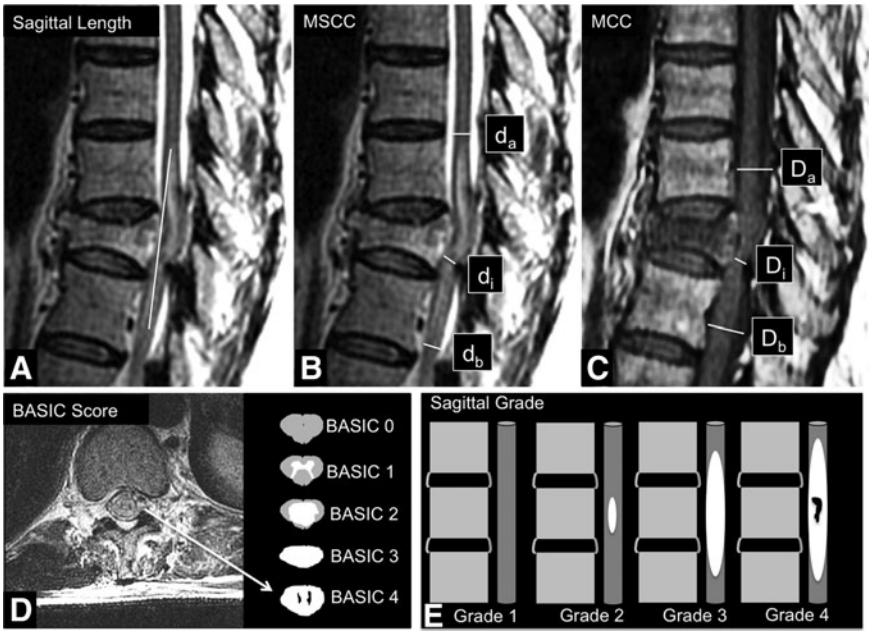

FIG. 1. Image analysis. (**A, B**) Sagittal T2-weighted magnetic resonance imaging (MRI) of the thoracic spine in a patient with acute SCI demonstrating how this sequence was used to measure the length of T2 signal hyperintensity in mm (white line in A) and tocalculate maximum spinal cord compression (MSCC) (B, (1-(d/((da+db)/2)) ×100%). (**C**) Sagittal T1-weighted image of the thoracic spine demonstrating how this sequence was used to measure MCC ((1-(D/((Da+Db)/2)) ×100%). (**D**) Axial T2-weighted MRI of the thoracic spine at the level of the epicenter of injury in a different patient. Foci of T2 hypointense hemorrhage are surrounded by hyperintense edema with no normal cord signal, consistent with BASIC grade 4; white arrow denotes associated cartoon depiction of Brain and Spinal Injury Center (BASIC) axial grade. (**E**) Cartoon of the sagittal grading system.

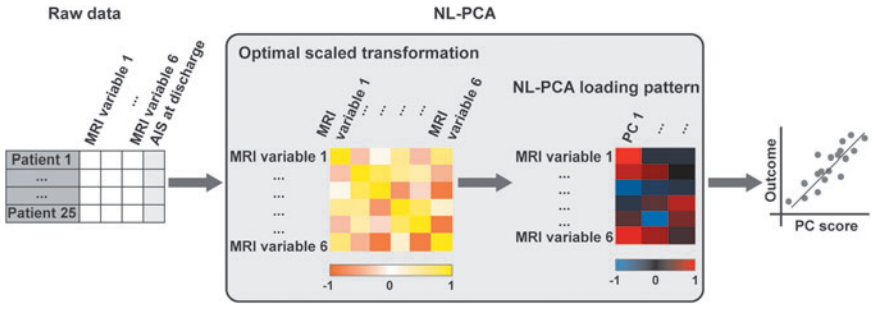

FIG. 2. Multidimensional analytical workflow. Raw magnetic resonance imaging (MRI) variables are fed into a nonlinear principal component analysis (NL-PCA). NL-PCA uses a process called optimal scaling transformation to handle different analysis levels (e.g., ordinal and numeric) in the dataset. Optimal scaling assigns quantitative values to categorical variables optimally, meaning maximizing the variance of the predefined number of principal components (PCs) (i.e., dimensions). The NL-PCA loading pattern shows the weight (i.e., loading) of every single MRI variable on the extracted PCs. In a next step, individual PC scores are used to define the predictive nature of PCs on outcome. An individual PC score is the sum of the multiplied loadings by the individual raw value of every single variable. AIS, American Spinal Injury Association (ASIA) Impairment Scale. Color image is available online at www.liebertpub.com/neu

Figure 2. NL-PCA is suitable for a set of variables including mixed measurement levels (nominal, ordinal, and numeric).[42,43] In NL-PCA, variables are assigned numerical values through an automated process called optimal scaling transformation. First, NL-PCA was applied using a six-dimensional solution. The final dimensionality (i.e., number of PCs) of the PCA was defined based on (1) Kaiser rule: eigenvalue >1 and (2), Cattell rule: scree plot.[44,45] The NL-PCA was then pruned with reduced PC dimensions.

To determine the stability of the NL-PCA solution, we performed a nonparametric balanced bootstrapping procedure using 2000 iterations and Procrustes rotation.[46] The two-dimensional NL-PCA solution was further cross-validated with the bootstrapped solution by using root mean square difference in PC loading patterns, the coefficient of congruence, the Pearson product moment correlation coefficient, and the Cattell salient variable similarity index. Convergence of these mathematically distinct metrics indicates consensus for replication of PC patterns.

The sensitivity of the extracted two-dimensional PC scores for predicting AIS at discharge was tested with a linear mixed model. To assess the bivariate relationship between AIS at discharge and MRI measures, separate Spearman rank correlations and an optimal scaled regression were applied. These procedures allow a direct comparison between the univariate correlations from individual variables and multivariable sets with different metric features (i.e., ordinal and numeric).

All predictive validity testing was based on individual MRI measures from MRI obtained near time of admission and AIS at time of patient discharge from the hospital. Statistical significance for all analysis was set at $\alpha = 0.05$. Bootstrapping and power calculations indicated that the $N = 25$ was sufficient for assessing the predictive validity of MRI with respect to AIS at discharge.

Levels of validity

Validation of MRI measures involves different levels of validity assessment as described by classical measurement theory. ''Face validity'' is defined as the concept that the MRI measures accurately reflect what they purport to measure on face value (i.e., an MRI-measured lesion looks like a lesion). ''Convergent validity'' is the concept that measures that should correlate, do indeed correlate (i.e., lesion length and lesion area do correlate). ''Discriminant validity'' refers to the concept that measures that should diverge, do indeed diverge (i.e., measures of ligamentous change diverge from neuroanatomical measures). ''Construct validity'' refers to the concept that multidimensional patterns are coherent from a theoretical perspective (i.e., neuroscores coalesce as coherent unit). Construct validity can be considered to involve both discriminant and convergent validity. ''Predictive validity'' refers to the concept that multidimensional MRI patterns can predict outcome. In the Results section, we address which level of validity is addressed by each statistical finding.

Results

Patient characteristics, MRI metrics, and TLICS scores for our cohort are presented in Table 1. Optimally scaled correlation revealed strong bivariate associations among MRI measures (Fig. 3A). NL-PCA analysis revealed that PC1–3 had high loadings by MRI scores (Fig. 3B). The Cattell and Kaiser criteria for PC retention converged on retention of a pruned two-dimensional PC solution (Fig. 3C). Re-extraction of NL-PCA restricted to two dimensions confirmed that PC1–2 accounted for 87.0% of the variance (64.3% and 22.7%, respectively) in imaging findings (Fig. 3D).

The bootstrapping results support the stability of the two-dimensional PCA solutions with only marginal changes in the total variance accounted for (total: 89.4%; PC1: 64.3%; PC2: 25.1%). Further, the loading pattern of the two-dimensional NL-PCA strongly agrees with the loading pattern of the bootstrapped PCA solution for both PC1 (root mean square difference = 0, coefficient of congruence = 1, Pearson product moment correlation coefficient = 1, and Cattell salient variable similarity index = 1, $p < 0.05$) and PC2 (root mean square difference = 0, coefficient of congruence = 1, Pearson product moment correlation coefficient = 1, and Cattell salient variable similarity index = 0.86, $p < 0.05$).

In the two-dimensional NL-PCA solution, all imaging variables loaded positively on PC1. MCC, MSCC, and TLICS also loaded positively on PC2 (variance orthogonal to PC1) while BASIC, sagittal grade, and longitudinal extent of injury loaded negatively on PC2. Together these results suggest that the PC1–2 reflect radiological tissue changes (face validity); that PC1 reflects agreement among MRI scoring schemes (convergent validity); and that PC1 and PC2 reflect distinct patterns, with PC2 reflecting divergence among two distinct blocks of scoring schemes (discriminant validity).

To better understand the discriminant nature of PC2, we projected individual patients into the PC1–PC2 biplot space (Fig. 4) and discovered that there appeared to be a broad dispersion of subjects within the PC space, suggesting the potential for distinct subpopulations. We hypothesized that spinal decompression surgery may account for the dissociations among patient distributions. Linear mixed model regression confirmed that spinal decompression

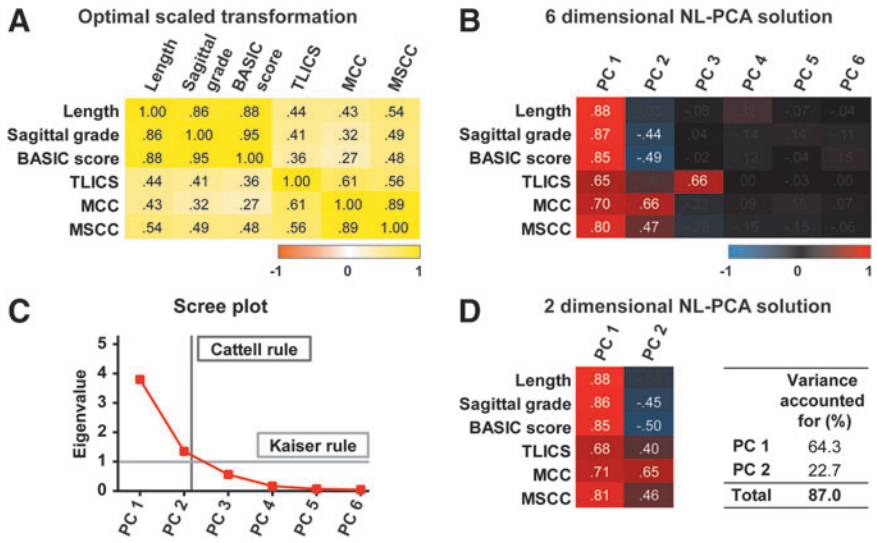

FIG. 3. Non-linear principal component analysis (NL-PCA) results demonstrate face validity, convergent validity, and construct validity. (**A**) Optimal scaled transformation matrix of all magnetic resonance imaging measures. (**B**) Six-dimensional NL-PCA solution loading patterns. Loadings $\geq|0.4|$ are emphasized in white. (**C**) Shows the scree plot for the six-dimensional NL-PCA. The Cattell and the Kaiser rules were applied to define the amount of components to retain for the final NL-PCA. The criteria converged on a two-dimensional solution, (**D**) Shows the re-extracted two-dimensional NL-PCA solution and the amount of variance accounted for by the two principal components (PCs). Loading values $\geq|0.4|$ are in white text. BASIC score, Brain and Spinal Injury Center score; TLICS, thoracolumbar injury classification system; MCC, maximum canal compromise; MSCC, maximum spinal cord compression. Color image is available online at www.liebertpub.com/neu

impacted PC2 scores ($F=25.4$, $p<0.0001$) but not PC1 ($p>0.05$). This suggests that PC2 may reflect MRI features associated with the clinical decision making process to perform spinal cord decompression. Careful re-examination of the loadings further supports this idea (Fig. 3D).

To test the predictive validity of PC1 and PC2 MRI ensembles, we used mixed model regression to test their association with AIS at discharge. Both PC1 and PC2 were statistically significantly related to AIS at discharge (PC1: $F=8.63$, $p=0.001$, eta squared $=0.55$, power $=0.98$; PC2: $F=3.28$, $p=0.041$, eta squared $=0.32$, power $=0.66$). PC1 specifically predicted AIS neurological impairment at time of patient discharge across the range of injuries in a monotonic fashion, with higher PC1 scores reflecting worse function (AIS A) and lower PC1 scores reflecting better function (AIS E) ($p<0.05$ by linear contrast; $p>0.05$ for quadratic).

PC2, on the other hand, had a narrower range of association with neurologic impairment, differentiating AIS A from other AIS grades ($p<0.05$) with no other statistical significance. Because of the retrospective nature of the study, AIS at discharge was chosen as the short-term outcome. To assess the relationship between PC1/PC2 and length of stay, a Pearson correlation was performed (PC1: Pearson $r=0.45$, $p=0.023$, and PC2 $r=-0.39$, $p=0.057$); this indicates that multidimensional MRI predicts length of stay, as a secondary validation end point.

To better understand the predictive validity of the individual MRI scores versus the PC1 and PC2 ensembles, we performed a nonparametric Spearman rank correlations of imaging variables with AIS at discharge (Table 3 and Fig. 5). BASIC score (rho $=-0.93$), sagittal grade (rho $=-0.85$), longitudinal extent of injury (rho $=-0.83$), and PC1 (rho $=-0.75$) were all negatively correlated with AIS at discharge. PC2 (rho $=0.49$) was mildly positively correlated with AIS at discharge, while TLICS, MCC, and MSCC were not statistically significantly correlated with AIS at discharge.

To confirm the comparative predictive validity results, we used an optimal scaled regression. This method provides a way to compare correlations between variables with different properties and distributions. BASIC was the only statistically significant ($p=0.001$) predictor of AIS at discharge in this multiple variable model. Because of multicolinearity, PC1 and PC2 were not included in the optimal scaling regression.

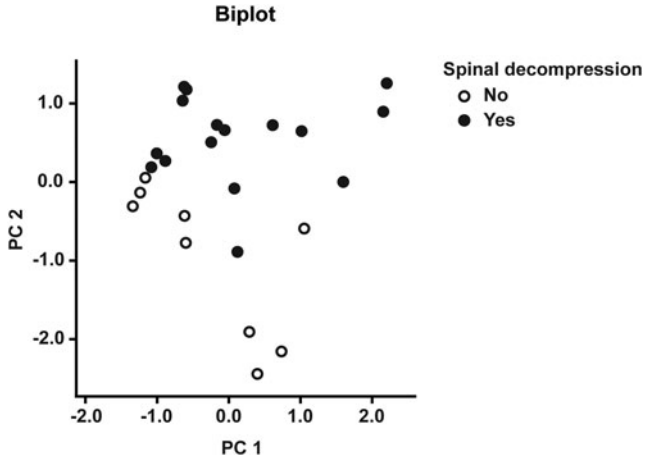

FIG. 4. Discriminant validity of principal component 2 (PC2). Individual subject's PC scores are plotted into the two-dimensional biplot space described by PC1 and PC2. Subjects who underwent surgical decompression (closed circles) after magnetic resonance imaging acquisition have higher PC2 scores than those who did not (open circles). The biplot highlights the discriminative validity of PC2.

Discussion

In this study, we assessed multiple MRI metrics of SCI, which were all predominately developed for use in the more common cervical SCI, here applied in thoracic SCI. TLICS, which is an

Table 3. Spearman Rank Correlation and Optimal Scaling Regression to Predict American Spinal Injury Association (ASIA) Impairment Scale at Discharge*

	Spearman correlation			*Optimal scaling regression*			
	Rho	*Rho squared*	*Sig*	*Zero-order*	*Partial*	*Part*	*Sig*
Length	–0.83	0.68	<0.001	–0.81	–0.09	–0.02	0.859
Sagittal grade	–0.85	0.73	<0.001	–0.67	0.65	0.16	0.514
BASIC score	–0.93	0.86	<0.001	–0.96	–0.92	–0.44	0.001
TLICS	–0.21	0.04	0.323	–0.11	–0.64	–0.15	0.203
MCC	–0.04	0.00	0.850	–0.17	0.30	0.06	0.405
MSCC	–0.20	0.04	0.351	–0.40	0.06	0.01	0.862
PC1	–0.75	0.57	<0.001				
PC2	0.49	0.24	0.014				

*Length of signal abnormality, sagittal grade, Brain and Spinal Injury Center (BASIC) score, and principal component (PC)1 are all negatively correlated with AIS at discharge while PC2 is positively correlated with American Spinal Injury Association (ASIA) Impairment Scale (AIS) at discharge. Optimal scaling regression identified BASIC score as the only statistically significant variable in this multiple variable model to predict AIS at discharge.

TLICS, thoracolumbar injury classification system; MCC, maximum canal compromise; MSCC, maximum spinal cord compression.

injury classification system for surgical decision making in thoracic spinal column injury and not a prognostic system, was also included to evaluate its relationship with the other imaging variables. TLICS does incorporate clinical data related to patient neurologic status in addition to imaging findings.

We used nonlinear principal components analysis to characterize the relationships of these variables and found two PCs accounting for 87.0% of the variance. All imaging variables loaded positively on PC1 (64.3% of the variance), which was highly related to AIS at discharge. MCC, MSCC, and TLICS also loaded positively on PC2 (22.7% of the variance), while variables concerning spinal cord signal abnormality loaded negatively on PC2. We found that PC2 was highly related to the patient undergoing surgical decompression.

BASIC, sagittal grade, and longitudinal extent of signal abnormality were all negatively correlated with AIS at discharge with the highest individual level of correlation for BASIC. In a multiple variable model, BASIC was the only statistically significant predictor of AIS at discharge, demonstrating that it most accurately predicted the variance of AIS at discharge in our study population. Our study provides evidence of convergent validity, construct validity, and clinical predictive validity for these imaging predominant measures of SCI when applied in acute thoracic SCI.

Variables involving spinal cord signal abnormality are highly related to each other and to AIS at discharge. By definition, these three variables are similar because they primarily consider the presence or absence of T2 signal hyperintensity in the spinal cord. The axial grading system (BASIC) and the sagittal grading system differ in their mild to moderate grades and direction of significance; however, both consider hemorrhage superimposed on edema as the highest grade. Otherwise, in the mild to moderate grades, BASIC is primarily concerned with the degree of spared white matter and the sagittal grading system is primarily concerned with single vertebral level versus multiple vertebral level edema. The sagittal grading

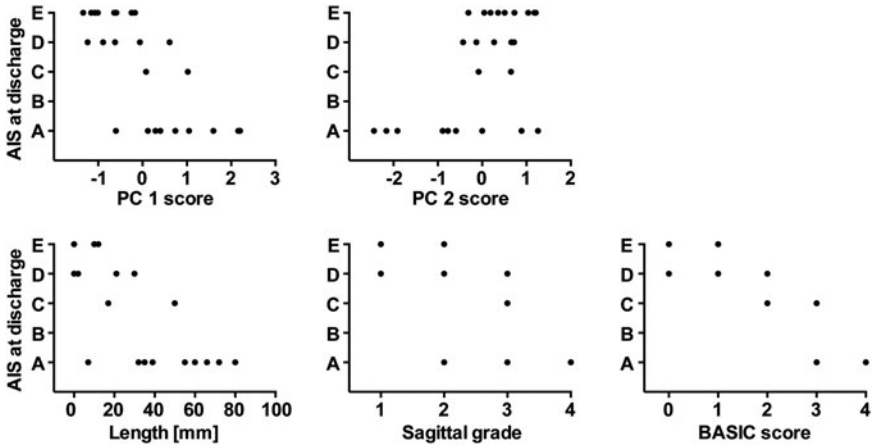

FIG. 5. Predictive validity. Scatterplots of American Spinal Injury Association (ASIA) Impairment Scale (AIS) at discharge with each statistically significant variable. Brain and Spinal Injury Center (BASIC) score had the highest individual level of individual correlation with AIS at discharge. BASIC score (rho = –0.927), sagittal grade (rho = –0.852), longitudinal extent of injury (rho = –0.825), and principal component (PC)1 (rho = –0.753) were all negatively correlated with AIS at discharge. PC2 (rho = 0.486) was mildly positively correlated with AIS at discharge, while thoracolumbar injury classification system, maximum canal compromise, and maximum spinal cord compression were not statistically significantly correlated with AIS at discharge. Note that because of the ordinal scale of the sagittal grade and the BASIC score, a number of subjects coincide on both x and y axes.

system (ordinal) and the longitudinal extent of T2 signal abnormality (numerical) are by definition similar concepts except that the sagittal grade also accounts for the presence of hemorrhage.

As expected, these variables grouped together on PC analysis and were positively correlated together providing evidence of convergent and construct validity and were negatively correlated with AIS at discharge providing evidence of clinical predictive validity. BASIC demonstrated the highest individual degree of negative correlation with AIS at discharge; however, all three metrics can be considered individually valid for predicting early neurological impairment in thoracic SCI.

The multiple variable model identified BASIC as the dominant imaging variable in predicting AIS at discharge, because it was the only statistically significant variable in the multiple regression model. This suggests that BASIC (a brief ordinal scale) most tightly captures AIS (also a brief ordinal scale) at discharge compared with the other measures.

MCC, MSCC, and TLICS grouped together with the other imaging variables on PC1 but diverged from the other imaging variables (of spinal cord signal abnormality) on PC2. Because PC2 was highly related to the patient undergoing spinal decompression and positively correlated with AIS at discharge, the relationship of these variables that loaded positively on PC2 (MCC, MSCC, TLICS) with AIS at discharge is thus quite complex. These three variables have variance with PC1 correlating negatively with AIS at discharge, and variance with PC2 correlating positively with AIS at discharge and being highly related to the likelihood of undergoing surgical decompression.

PC2 thus may capture some of the nuances of surgical decision-making reflected in TLICS whereby an incomplete SCI at admission receives a higher individual scoring than a complete SCI. The particular phenotype captured by a high PC2 score would be a patient with a high MCC, MSCC, and TLICS but lower scores on measures of cord signal abnormality; a patient with an unstable spine and compression but a relatively preserved spinal cord.

The fact that MCC and MSCC did not individually have a significant correlation with AIS at discharge is consistent with previous literature examining measures of spinal canal stenosis with thoracolumbar SCI outcomes and may reflect the complexity of their relationship with both surgical decision making and subsequent early neurological impairment.[47] The strong negative correlations between direct MRI measures of SCI (BASIC score, sagittal grade, and longitudinal length of T2 signal hyperintensity) and clinical outcomes suggests incorporation of these measures into surgical decision-making tools may be helpful. Defining valid imaging biomarkers for thoracic and thoracolumbar SCI is critically important because the thoracic spinal cord has been proposed as the most suitable region for initial invasive clinical trials targeting SCI.[48,49]

Our study has several limitations mostly related to the retrospective technique and relatively small sample size. Our retrospective technique allowed us to effectively study the relatively rare thoracic SCI in an efficient manner but did limit the clinical variables to those already collected in routine clinical care. The retrospective nature of this study also limits our control over timing of MRI after injury.

Leypold and colleagues[50] have shown that the longitudinal extent of T2 hyperintensity can increase by up to one vertebral body height per day in the acute stage of injury. Our institution routinely obtains MRI early after injury, and 88% (22/25) were performed within 24 h of injury, thus limiting the effect of delayed timing on extent of T2 hyperintensity. Future prospective controlled experiments would ideally control for variables such as hemodynamic support, timing of surgical decompression, steroid therapy, and timing of MRI after injury with longer-term clinical follow-up and a larger number of patients. Importantly, our study does suggest that any prospective collection of data in thoracic SCI should include metrics of spinal cord signal abnormality on MRI as measured in this study.

Another limiting factor is the use of AIS grade as a fairly coarse primary outcome measure for thoracic SCI in our cohort. Because of the retrospective nature of this study, more granular outcome measures, such as functional independence measure (FIM), were not available for analysis. Although the significance of AIS grade has been questioned in thoracic SCI, Lee and colleagues[51] recently showed that AIS grade changes are associated with significant functional benefit relative to FIM scores and ambulation in a retrospective analysis of a large longitudinal database of patients with thoracic SCI.[52]

Structural MRI findings correlated with early impairment with varying resolution, depending on the scoring scheme (e.g., BASIC vs. sagittal grade). Multiple regression analysis confirmed that most of the univariate MRI assessments were noisy correlates of functional impairment, with the sole exception of the BASIC score. In testing theory, this class of evidence is referred to as predictive validity, and it directly addresses whether a set of measurements (MRI features) have value for predicting a separate outcome domain (AIS grade) at a later time.

Our application of NL-PCA directly assessed whether the multidimensional ensemble of spinal cord MRI features performs better than each individual outcome. NL-PCA is a rigorous and appropriate approach for performing multivariate pattern-detection to compare the relative merits of multiple scales that purport to measure the same underlying features (in this case, structural MRI features). This approach has a long history in physics, human performance testing, and other disciplines dating back more than a century.[53,54]

Although it is currently unusual to have such advanced analytics applied in the clinic, applications like the one here promise to be a central feature of the emerging field of ''precision medicine,'' where analytics will be integrated in clinical decision making.[55,56] Accordingly, several very recent articles incorporate NL-PCA as a precision medicine tool in both pre-clinical and clinical SCI.[57–59] The present findings suggest that multidimensional MRI features of the thoracic spinal cord may have relevance for clinical issues such as patient stratification for diagnosis, intervention planning, and clinical trial criteria. Further work is needed, however, to test the capacity of structural MRI to predict long-term outcome.

Conclusion

This study validates the use of BASIC and other MRI measures of acute SCI specifically in the setting of thoracic SCI. PC analysis identified two distinct patterns of variance: PC1, which was highly related to AIS at discharge, and PC2, which was highly related to surgical decompression. The highest individual correlation with AIS at discharge was seen with the BASIC system, although all metrics of spinal cord signal abnormality had a high degree of individual negative correlation with AIS at discharge. The relationship of MCC and MSCC with AIS at discharge was found to be more complex, likely reflecting the use of these metrics along with TLICS in surgical decision making. A multiple variable regression model identified BASIC as the only statistically significant predictor of AIS at discharge, signifying that BASIC best captured the variance in AIS within our study population.

Acknowledgment

This work was supported by R01NS067092 (ARF), the Craig H. Neilsen Foundation (ARF; JCB), Wings for Life Foundation (ARF), DOD grant CDMRP SCIRP 120559 (W81XWH-13-1-0297) (MSB and JCB). MCM was supported by an NIH T32 Fellowship, 5T32EB001631-10. JH was supported by a Craig H. Neilsen Foundation fellowship (313739).

Author Disclosure Statement

Dr. Talbott is a member of the data monitoring committee for StemCells, Inc.; Dr. Ferguson is an *ad hoc* consultant for Acorda Therapeutics. For the remaining authors, no competing financial interests exist.

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Address correspondence to:
Jason F. Talbott, MD, PhD
Department of Radiology
San Francisco General Hospital
1001 Potrero Avenue, Room 1X57C
San Francisco, CA 94110
or
Adam R. Ferguson, PhD
Neurological Surgery, Box 0899
UCSF Brain and Spinal Injury Center
1001 Potrero Avenue, Building 1, Room 101
San Francisco, CA 94143

E-mail: Jason.talbott@ucsf.edu;
adam.ferguson@ucsf.edu

nature COMMUNICATIONS

ARTICLE

Received 1 Jun 2015 | Accepted 6 Sep 2015 | Published 14 Oct 2015

DOI: 10.1038/ncomms9581 OPEN

Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury

Jessica L. Nielson[1], Jesse Paquette[2], Aiwen W. Liu[1], Cristian F. Guandique[1], C. Amy Tovar[3], Tomoo Inoue[4], Karen-Amanda Irvine[5], John C. Gensel[6], Jennifer Kloke[7], Tanya C. Petrossian[8], Pek Y. Lum[9], Gunnar E. Carlsson[7,10], Geoffrey T. Manley[1], Wise Young[11], Michael S. Beattie[1], Jacqueline C. Bresnahan[1] & Adam R. Ferguson[1,12]

Data-driven discovery in complex neurological disorders has potential to extract meaningful syndromic knowledge from large, heterogeneous data sets to enhance potential for precision medicine. Here we describe the application of topological data analysis (TDA) for data-driven discovery in preclinical traumatic brain injury (TBI) and spinal cord injury (SCI) data sets mined from the Visualized Syndromic Information and Outcomes for Neurotrauma-SCI (VISION-SCI) repository. Through direct visualization of inter-related histopathological, functional and health outcomes, TDA detected novel patterns across the syndromic network, uncovering interactions between SCI and co-occurring TBI, as well as detrimental drug effects in unpublished multicentre preclinical drug trial data in SCI. TDA also revealed that perioperative hypertension predicted long-term recovery better than any tested drug after thoracic SCI in rats. TDA-based data-driven discovery has great potential application for decision-support for basic research and clinical problems such as outcome assessment, neurocritical care, treatment planning and rapid, precision-diagnosis.

[1] Department of Neurosurgery, Brain and Spinal Injury Center, University of California, San Francisco, 1001 Potrero Avenue, Building 1, Room 101, San Francisco, California 94143, USA. [2] Tagb.io, 1 Quartz Way, San Francisco, California 94131, USA. [3] Department of Neuroscience, Ohio State University, 460 West 12th Avenue, 670 Biomedical Research Tower, Columbus, Ohio 43210, USA. [4] Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai city, Miyagi prefecture 980-0856, Japan. [5] Department of Neurology, San Francisco VA Medical Center, University of California San Francisco, San Francisco, California 94110, USA. [6] Department of Physiology, Spinal Cord and Brain Injury Research Center, Chandler Medical Center, University of Kentucky Lexington, B463 Biomedical & Biological Sciences Research Building, 741 South Limestone Street, Kentucky 40536, USA. [7] Ayasdi Inc., 4400 Bohannon Drive Suite #200, Menlo Park, California 94025, USA. [8] GenePeeks, Inc., 777 Avenue of the Americas, New York, New York 10001, USA. [9] Capella Biosciences, 550 Hamilton Avenue, Palo Alto, California 94301, USA. [10] Department of Mathematics, Stanford University, Building 380, Stanford, California, 94305, USA. [11] Department of Cell Biology and Neuroscience, W.M. Keck Center for Collaborative Neuroscience, Rutgers University, Piscataway, New Jersey 08854, USA. [12] Department of Neurosurgery, San Francisco VA Medical Center, University of California San Francisco, San Francisco, California 94110, USA. Correspondence and requests for materials should be addressed to A.R.F. (email: adam.ferguson@ucsf.edu).

Bioinformatics approaches for precision medicine are gaining momentum as biomedical researchers grapple with overwhelming amounts of data generated by all areas of science in the era of 'big-data'[1,2]. The central nervous system (CNS) injury literature seeks to understand the multifaceted effects of injuries to the brain and spinal cord by collecting high-volumes of detailed information on individual subjects, ranging from histological, physiological and bio-behavioral outcomes to health records from therapeutic trials. The sheer volume of data presents a problem for managing and interpreting therapeutic findings without computational assistance[3–5]. Informatics tools are currently being developed in preclinical and clinical CNS injury studies[6,7], and resources such as the Neuroscience Information Framework (NIF, http://www.neuinfo.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) offer user-friendly query interfaces to bridge knowledge that exists in biomedical research. However, there remains a lack of user-friendly statistical integration and visualization tools that can be applied to primary research data from multifaceted CNS disorders.

In this sense, translation of basic research into clinical therapeutics can be conceptualized as a big-data integration issue. Thousands of studies have been published aiming to characterize spinal cord injury (SCI) and traumatic brain injury (TBI) from a basic scientific view point, yet we still do not fully understand these complicated disorders. In addition, few therapies have navigated successfully through clinical trials into standards for patient care[8–10]. The emerging field of precision medicine seeks to apply analytics and data-visualization tools[3,4] to improve understanding and treatment of complex disorders such as SCI and TBI[11].

The present study applies a data-analytic approach, topological data analysis (TDA)[12], for improved discovery of fundamental syndromic injury patterns and assessment of precision therapeutic targeting from preclinical drug trials in SCI and TBI. TDA couples unsupervised pattern detection[13] and network visualization[12] to rapidly extract the full syndromic injury disease taxonomy from the full set of inter-correlated biological, behavioral and health outcomes in diverse SCI[14] and TBI[15] animal research data. Harnessing a TDA framework, data-driven navigation of the syndromic space is performed by rapid colour-based re-mapping of individual outcomes onto the network to improve interpretation of histopathology, functional recovery and experimental therapeutic effects. TDA helps facilitate the identification of novel relationships in complex, heterogeneous data sets, allowing for data-driven hypothesis generation that may uncover mechanisms for increased morbidity following SCI and TBI. TDA uncovered location-specific impact of SCI and TBI polytrauma on recovery of forelimb function, and differential sensitivity of forelimb measures and locomotion measures in cervical SCI. Application of TDA to preclinical therapeutic trials revealed irreproducible efficacy of methylprednisolone (MP) and minocycline treatment between cervical and thoracic SCI, yet uncovered the novel discovery that perioperative hypertension predicts worse neurological recovery following thoracic SCI.

Results

Initial attempts to visualize the syndromic space following CNS injury in rodents and nonhuman primates have revealed proof-of-concept multivariate relationships of tissue pathology and functional recovery, with each dimension showing specific sensitivity to different injury models[13,14,16]. Visualizing the syndromic space through traditional methods such as principal components analysis (PCA) requires database querying, statistical coding and graphical programming. These requirements disempower basic researchers and clinicians by limiting rapid and actionable access to syndromic findings (Fig. 1a,b). In contrast, TDA can apply PCA through singular value decomposition (SVD) to reveal the complex multivariate relationship of all predictor and outcome variables simultaneously as a network diagram, where similar individuals are clustered into nodes, and clusters that share one or more individuals are joined by an edge (Fig. 1c). The full syndromic topological map provides a platform for rapid and intuitive exploration of the data set in an unbiased, data-driven manner (Fig. 1d). Once the network is generated, the shape of the data set can be investigated to understand the relationship of each variable across the topological syndromic space to identify groups of clustered individuals that can be further probed for specific relationships among outcomes, validation and targeted hypothesis testing.

TDA uncovers complex SCI and TBI outcome by injury location. To test the application of TDA to CNS injury research, we assessed the syndromic network topology of a recently developed rodent model of combined SCI and TBI. The results of the functional and histopathological deficits of this model have been described at the univariate level[15], with only a subset of endpoints reaching significance (Fig. 2, bar graphs), leading to potentially unclear conclusions about outcome. TDA combined with SVD rapidly re-evaluated the findings across all endpoints simultaneously. Subjects were mapped into the network based on functional (Fig. 2a,b; Supplementary Software 1, dropdown) and histopathological outcomes (Fig. 2c,d; Supplementary Software 1, dropdown), showing a distinct separation of each injury model into sub-networks (Fig. 2e; Supplementary Software 1, dropdown). Sham and TBI-only subjects clustered into distinct regions in the network. SCI-only subjects and SCI + TBI contralateral to each other clustered together into a separate sub-network in the topology, demonstrating worse outcome than the other injury groups (Supplementary Software 1, dropdown). In contrast, subjects with SCI + TBI on the ipsilateral side (Fig. 2, circled) clustered near the sham condition in a sub-network that mapped to better performance on measures of forelimb function (Fig. 2a; Supplementary Software 1, dropdown). This multidimensional difference between ipsilateral and contralateral TBI occurred despite equally-sized lesions (Fig. 2b; Supplementary Software 1, dropdown). Although the univariate effects of lesion location were subtle and varied in their statistical significance across endpoints, (Fig. 2a,c), TDA uncovered a dramatic multidimensional effect when the full ensemble of endpoints was used to render the full syndromic space. Together, these TDA findings reveal the clear separation of syndromic features of compound injuries according to location, providing a proof-of-concept for application of TDA in poly-traumatic CNS injury.

TDA reveals forelimb outcomes most sensitive to cervical SCI. To test the application of TDA combined with SVD to SCI, we assembled raw data from several common SCI models, including hemisections, weight-drop and force-driven hemi-contusion injuries to the cervical spinal cord (Fig. 3; Supplementary Software 2, dropdown). Grooming behaviour and paw preference in a cylinder reveal graded levels of recovery (Fig. 3a), that map to lesion size, tissue sparing and deformation (Fig. 3b; Supplementary Software 2, dropdown). However, measures of open-field locomotion for both forelimb (Fig. 3a; Supplementary Software 2, dropdown) and hindlimb (Supplementary Software 2, dropdown) do not show much variability in recovery of function. In the syndromic topology, grooming function has the strongest visual mapping to lesion size (Fig. 3b; Supplementary Software 2,

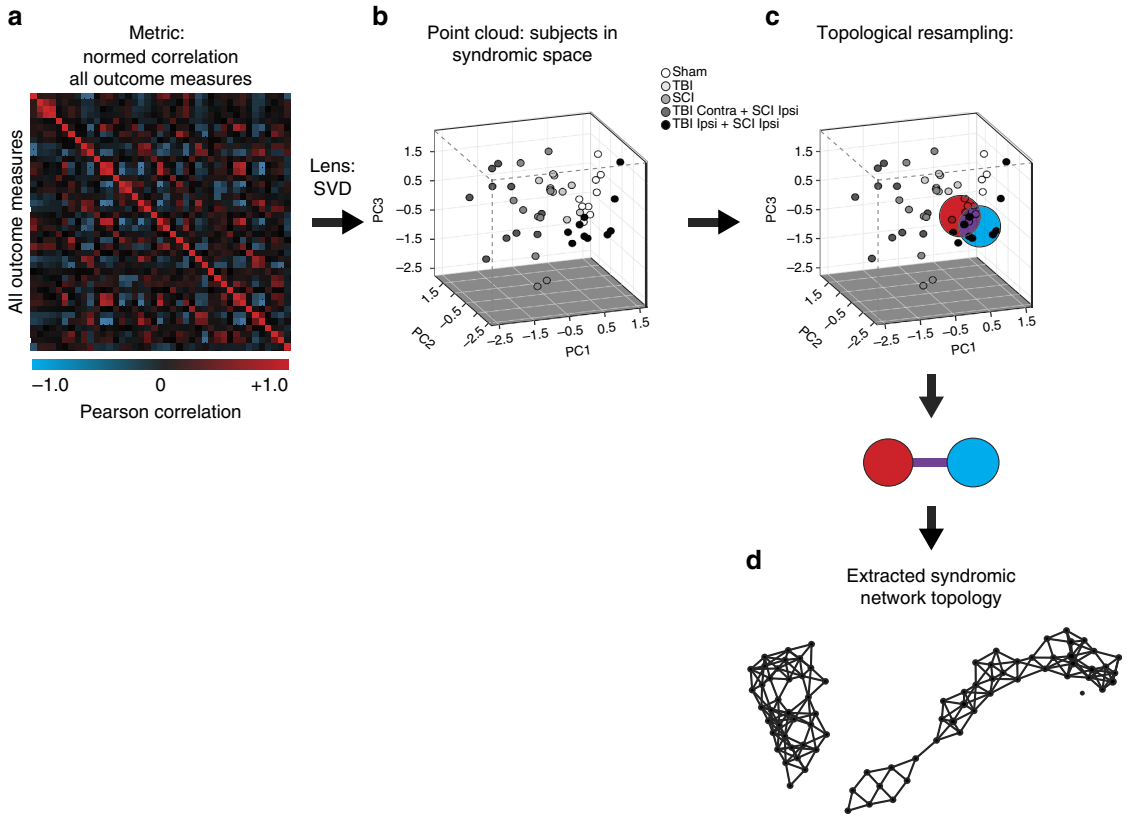

Figure 1 | Topological representation of the syndromic space using TDA. (**a**) Data sets containing functional and histological outcomes were analysed using TDA from a bivariate correlation matrix of all outcomes. (**b**) Data were processed with the principal and secondary metric singular value decomposition (SVD) lens to generate the syndrome space. (**c**) TDA resamples the syndromic space many times to link subjects into nodes (red/blue circles) and connects overlapping subjects with edges (purple line) (**d**) to create a robust network topology for rapid visualization and interpretation of outcomes over time.

dropdown), whereas recovery of paw preference in the cylinder shows a stronger visual mapping with white matter sparing. Little to no variability is seen in the hindlimb open field (Supplementary Software 2, dropdown), most likely because it was designed to measure hindlimb coordination following bilateral thoracic injuries[17], whereas these subjects received various grades of unilateral cervical injuries. There was some variance in the measure of forelimb open field for the most severe injuries (Fig. 3a, circle), however, it did not map to the full range of lesion pathology. TDA enabled rapid multivariate visualization of group differences with a quicker turn-around for interpretation.

Differential mapping of injuries in the syndromic network. To understand how injury models map onto the SCI syndromic space, we recoloured the network using categorical experimental SCI groups (Fig. 3c; Supplementary Software 2, dropdown: sham, hemisection, contusion and so on), and observed biomechanical tissue deformation (μm) measured at the time of injury by servo-feedback position detectors on the SCI contusion devices (Fig. 3b; Supplementary Software 2, dropdown). Each injury group occupies a distinct section of the network (Supplementary Software 2, sham, hemisection, 75 kdyn and 100 kdyn force-driven contusions[18]; 6.25 mm and 12.5 mm weight-drop contusions[19]; red nodes), validating TDA syndromic comparisons of pathology and function across multiple injury models. Mapping tissue changes onto the network (Fig. 3b; Supplementary Software 2, dropdown) confirmed that tissue changes vary as a function of injury group (Fig. 3c; Supplementary Software 2, dropdown) and predict subject positions within the full syndromic network space (Supplementary Software 2). Lesion size shows less variability between the different injury models, with the exception of the most severe 12.5 mm contusions (Supplementary Software 2, dropdown). These larger lesions are confirmed visually in the network, where larger lesion pathology corresponds to 12.5 mm weight-drop injuries and 100 kdyn force-driven injuries. White matter sparing (Fig. 3b; Supplementary Software 2) shows a wide range of graded severities for the contusion injuries (weight drop and force driven), and hemisection injuries show a substantial loss in white matter (Supplementary Software 2, dropdown). This pattern is confirmed in the network, with the distribution of nodes with the most white matter sparing appearing on the perimeter of the bottom flare. Motor neuron (MN) sparing along the rostro-caudal axis of the lesion (Supplementary Software 2, dropdown) is the histological feature most sensitive to injury in this data set; nearly all of the contusion subjects had large-scale loss of MNs, even with the mildest of injuries. This sensitivity of MN loss is visually reflected in the network topology where only the shams and hemisection regions of the flares show MN sparing (Supplementary Software 2, dropdown), illustrating the vulnerability of this cell type to contusive spinal cord damage.

Visually guided data exploration uncovers drug effects. We identified the nodes within the topology that stood out as having poor functional recovery on grooming and forelimb open field (Fig. 3a, circles), despite nodes in this region showing less-severe

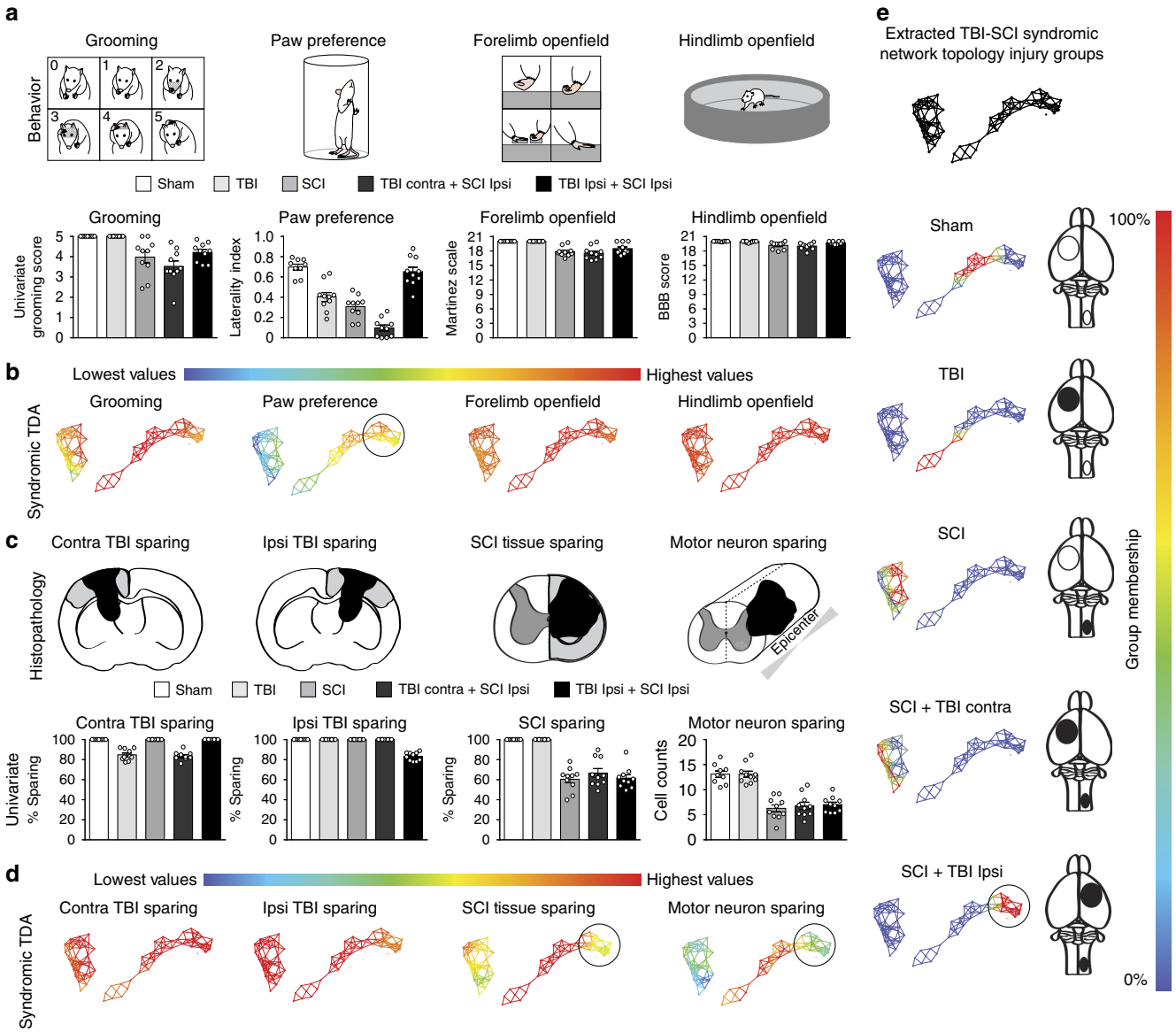

Figure 2 | Histo-behavioural network topology of combined TBI-SCI model. (**a,b**) Behavioral outcomes of forelimb function and (**c,d**) histopathology were mapped onto the topological network using TDA. Data from this model shows a distinct recovery pattern depending on whether the combined TBI is contralateral (contra) or ipsilateral (ipsi) to the SCI. (**e**) Each injury group occupies a distinct region of the network topology, highlighted as red nodes for 100% enrichment (heat map) for each particular injury model. Sham controls ($n=9$) and TBI-only ($n=10$) subjects are located in the right cluster. SCI-only ($n=10$) and SCI + TBI contra ($n=10$) are both located in the left cluster. SCI + TBI ipsi ($n=10$) interestingly are grouped next to the sham subjects in the right cluster (circled part of the network), due to a syndromic functional recovery similar to shams (**a**), despite showing no difference in pathology compared with subjects with SCI alone or SCI + TBI contra (**c**). All outcome averages and injury models were exported into an HTML figure (Supplementary Software 1) for rapid visualization and user-guided exploration of the syndromic topological space in this data set.

injuries based on the degree biomechanical tissue deformation (Fig. 3b, circle). This sub-network was also significantly enriched for 12.5 mm weight-drop contusions, yet we noticed that not all injuries of this type performed so poorly. To probe factors that might contribute to abnormally bad function, we drilled into this effect. We compared subjects in these nodes with 12.5 mm contusions that performed well on forelimb open field using a ranked Kolmogorov–Smirnov (KS) test. The ranked KS test is analogous to a gene-set enrichment analysis here applied to identify predictor and outcome metric sets (rather than gene sets) that are most sensitive to group conditions (hypothesis testing)[20]. KS tests between nodes within the high and low functioning groups uncovered an external predictor (not included in the generation of the network) that could account for functional differences: subjects were part of a preclinical trial of two anti-inflammatory drugs: minocycline and MP and no-drug controls. The network was then recoloured based on treatment condition to highlight nodes enriched for drugs and 12.5 mm weight-drop contusions (Fig. 3d, red nodes, 'no-drug' control ($n=11$ original subjects; pure nodes $=7$, $n=8$), minocycline ($n=11$ original subjects; pure nodes $=4$, $n=6$) and MP ($n=10$ original subjects; pure nodes $=2$, $n=4$)). KS test results comparing treatment groups enriched in the network suggested significant differences on several outcomes based on t-test and KS test P values between groups ($P<0.05$; Fig. 3e) in the TDA-identified 'responder' subjects. To independently confirm this, we performed a one-way analysis of variance (ANOVA) on the TDA-identified subject subsets, confirming significant drug effects on MN sparing

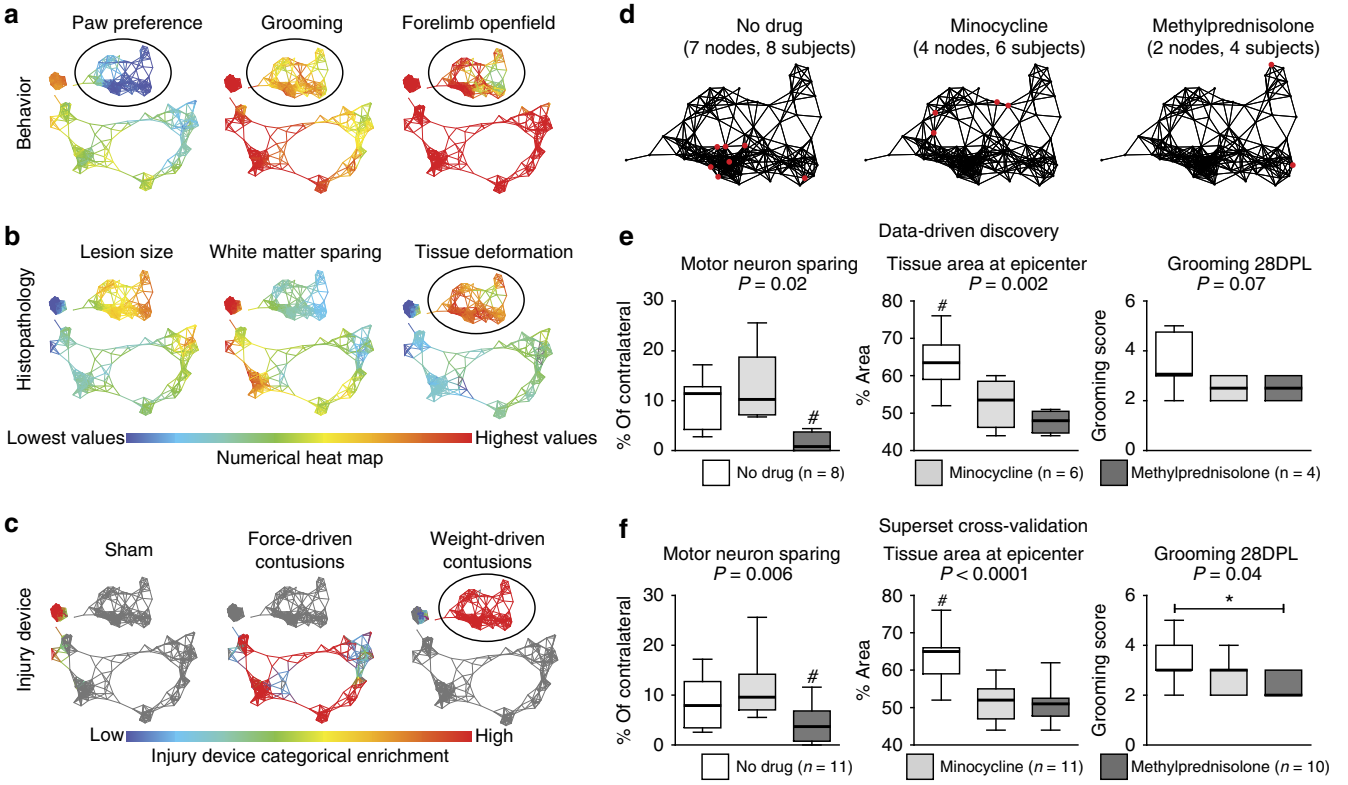

Figure 3 | Data-driven discovery of deficits in rats in cervical SCI drug trials. (**a**) Behavioural deficits in forelimb function were identified in the syndromic network (circled area). (**b**) Visual mapping of histopathology patterns in the network did not identify similar patterns to explain behavioral deficits, despite less tissue deformation in this portion of the network. (**c**) Enrichment for injury condition revealed these subjects were given the same type injury (weight-drop contusions, 12.5 mm, Supplementary Software 2). Data-driven exploration of these subjects within the network identified a no-drug controlled trial of minocycline and methylprednisolone (MP). (**d**) Nodes containing subjects significantly enriched for respective drug condition, and 12.5 mm weight-drop injuries were isolated (red nodes) for group comparisons using the Kolmogorov–Smirnov test (KS test). (**e**) The three outcomes with the smallest *P* values from the KS test results were identified in the sub-selection of subjects identified for each treatment condition. Results revealed significant MN loss in subjects receiving MP ($n=2$ nodes, 4 subjects) compared with minocycline ($n=4$ nodes, 6 subjects) and no-drug controls ($n=7$ nodes, 8 subjects) ($P=0.02$, $F(2,15)=5.21$, $\eta^2=0.41$, $1-\beta=0.74$), and significantly less tissue area at the injury epicentre in both minocycline and MP-treated subjects, compared with no-drug controls ($P=0.002$, $F(2,15)=10.02$, $\eta^2=0.57$, $1-\beta=0.96$). Non-significant functional deficits in grooming were observed 28 days post lesion (DPL) ($P=0.07$, $F(2,15)=3.18$, $\eta^2=0.30$, $1-\beta=0.52$). (**f**) Validation of these significant detrimental treatment effects were found in the entire superset of subjects for both MN sparing ($P=0.006$, $F(2,29)=6.08$, $\eta^2=0.30$, $1-\beta=0.85$) and total tissue area at epicentre ($P<0.0001$, $F(2,29)=19.94$, $\eta^2=0.60$, $1-\beta=1.0$), and grooming at 28 DPL was also significant ($P=0.04$, $F(2,29)=3.68$, $\eta^2=0.20$, $1-\beta=0.63$). Box and whisker plots show mean and minimum/maximum range of values. *P* values represent overall treatment effect using one-way ANOVA. *Post hoc* pairwise comparisons between each drug condition identified significant decreases in MN sparing in MP-treated subjects, and more tissue area in no-drug controls ('#',significantly different from both groups; $^*P<0.05$). All outcomes at each time point, location of injury conditions and treatment groups are mapped onto the HTML network Supplementary Software 2.

($P=0.02$) and tissue area at the epicentre ($P=0.002$), with other outcomes approaching significance, including grooming at 28 days post lesion (DPL) ($P=0.07$). The effect size (η^2) and power calculation ($1-\beta$) values (detailed in Fig. 3e legend) suggest that the TDA-identified subset of subjects and outcome metrics for each group had 'large' effect sizes[21], yielding high power, despite the limited *n* in the subpopulations of interest. *Post hoc* means testing was performed on significant main effects of treatment using pairwise comparisons between all treatment conditions with multiple-comparison correction. MP-treated subjects had significantly less MN sparing compared with both no-drug controls ($P=0.03$) and minocycline-treated subjects ($P=0.006$), but no difference in MN sparing was found between no-drug and minocycline treatment groups ($P=0.33$). For total tissue area at epicentre, control subjects showed significantly greater tissue compared with both MP ($P=0.001$) and minocycline ($P=0.006$) subjects, but no difference in tissue area was found between MP and minocycline ($P=0.24$). These statistical results suggest that MP significantly reduced MN sparing, and both MP and minocycline impacted total tissue area at the epicentre. After interviewing the original data donors, we discovered that data from this drug trial was not previously published because treatments were thought not to show functional benefits (the 'file-drawer phenomenon').

The TDA-identified subpopulation analysis suggested that minocycline and MP had effects on a subset of endpoints, in a subset of the individuals. To confirm the generality of these effects, we next tested for the effects of minocycline and MP on MN sparing, total tissue area and grooming function on the full data set ('superset cross-validation') from this drug trial (Fig. 3f). One-way ANOVA and *post hoc* testing of individual treatment groups was performed with the same criteria as the comparisons in Fig. 3e. Results confirmed a significant main treatment effect for MN sparing ($P=0.006$), with the MP group showing significantly less MN sparing than either minocycline ($P=0.002$) or no-drug controls ($P=0.04$), but not between

no-drug and minocycline ($P=0.21$). Total tissue area at the epicentre also had a main treatment effect ($P<0.0001$), with no-drug controls showing significantly more total tissue compared with both minocycline ($P<0.0001$) and MP ($P<0.0001$) groups, but not between minocycline and MP ($P=0.79$) groups. Last, grooming function at 28 DPL had a significant main treatment effect ($P=0.04$), with the MP group showing significant functional deficits compared with no-drug controls only ($P=0.02$), with non-significant grooming deficits found in minocycline compared with no-drug controls ($P=0.06$) or MP ($P=0.49$). Together this suggests that MN sparing and tissue area at the epicentre were the major drivers of the network-detected effects, with more modest contributions by other variables.

Conflicting cross-validation and irreproducible drug effects. TDA-based data-driven discovery revealed a hidden finding in legacy data that MP was potentially detrimental in cervical SCI. To test whether the same might be true in thoracic SCI, we pooled data from the VISION-SCI database[14] containing other subjects that were part of controlled MP drug trials. A previously conducted trial from the Multicenter Animal Spinal Cord Injury Study (MASCIS)[19] was identified, which contained a larger cohort of subjects (1996, $N=72$). TDA was performed using the same PCA/SVD lens and norm correlation metric used on the cervical data set (Fig. 3; Supplementary Software 2, dropdown) to cross-validate the detrimental effects of MP on this independent thoracic data set. Identification of nodes in the thoracic network receiving either vehicle control or different doses of MP (coded as MP1, MCP in Supplementary Software 3, dropdown) did not show the same detrimental effects in either functional recovery measured by locomotion with the BBB or tissue sparing at the injury epicentre (Supplementary Software 3, dropdown). A separate analysis on the same data set using TDA was performed with the L-infinity centrality lens, which attempts to cluster subjects in the network based on maximal distance between subjects and how far they are from the group norm[12]. TDA revealed that subjects were distributed along three main flares in the network. Identification of nodes enriched for either vehicle (Fig. 4a) or MP-treated subjects (Fig. 4b) revealed that a maximum of 50% group membership was represented in the red nodes in the network. Location of these nodes for each treatment condition within the network was visually mapped to functional recovery of BBB (Fig. 4c) and tissue sparing at the injury epicentre (Fig. 4d). Querying all subjects within this trial that received either vehicle control ($N=10$) or MP ($N=12$) did not show significant group difference on either BBB locomotor recovery (Fig. 4e, $P=0.73$) or tissue sparing at the epicentre (Fig. 4f, $P=0.15$). The results suggest that MP treatment had no significant effect in the thoracic SCI, in contrast to the deleterious effect observed in the cervical SCI trial (Fig. 3; Supplementary Software 2, dropdown). On the whole, these previously unpublished preclinical findings seem to confirm the lack of definitive data from preclinical trials of MP in SCI.

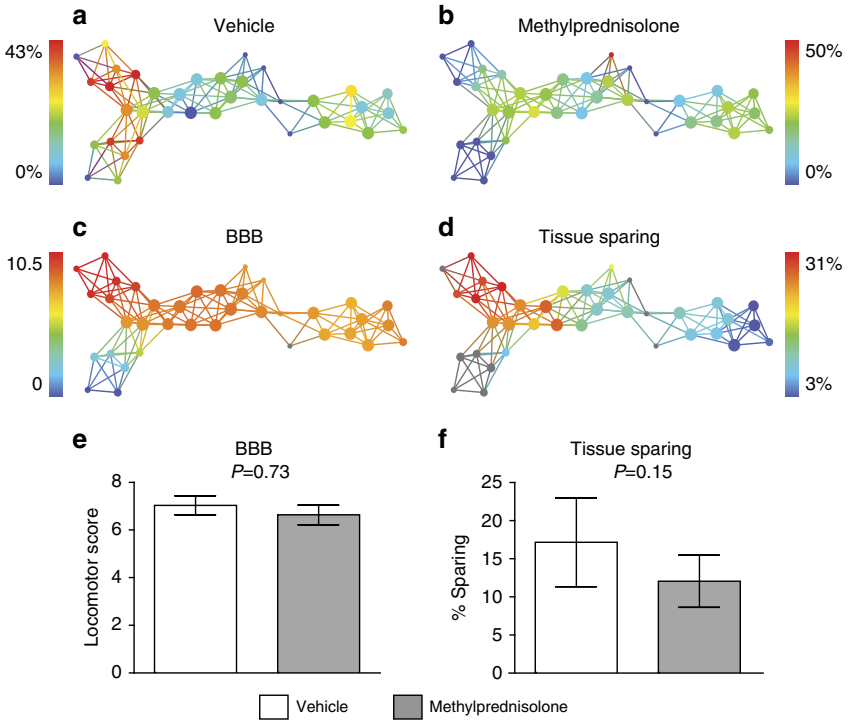

Figure 4 | Cross-validation attempt of MP in thoracic SCI L-infinity centrality network. TDA was performed on data mined from the VISION-SCI repository, queried based on subjects that were part of treatment trials testing MP (MP1 and MCP) following SCI ($N=72$). Location of treatment groups within the network for either (**a**) vehicle-treated control or (**b**) MP-treated subjects are shown, however, no nodes were 100% pure for either treatment condition, suggesting treatment was not a significant predictor of placement of subjects within this network. (**c**) BBB recovery and (**d**) total tissue sparing at the injury epicentre were mapped into the network to identify the range of recovery in this data set (red = better recovery, blue = worse recovery). Grouping subjects in the data set based on treatment condition did not reveal the same significant deficits observed in the cervical trial for MP for either (**e**) recovery of locomotor recovery measured by the BBB ($P=0.73$), or (**f**) the total tissue sparing at the epicentre ($P=0.15$). However, there was a trend towards less tissue sparing in subjects that received MP, similar to histopathology observed in cervical SCI (Fig. 3). The most striking difference in the network were subjects who had very large differences in tissue sparing along the top arm of the network, yet showed similar ranges of BBB functional recovery, which are explored further in Fig. 5. Histograms plotted as mean ± s.e. Student *t*-test used for significance testing between treatment groups.

Data-driven discovery that hypertension predicts dysfunction. Application of TDA in the context of cross-validation testing of MP treatment following thoracic SCI revealed an unexpected and much stronger predictor of neurological recovery than any of the drug conditions. Visually guided exploration of TDA sub-networks uncovered unusually large differences in functional recovery on the BBB locomotor scale in putatively identical injury severities. We isolated these disparate subject populations and categorized them into groups for further comparisons (Fig. 5a, circles). Nodes containing subjects that received identical 25 mm weight-drop contusions were grouped and compared with a KS test to identify measures that significantly differed between these two groups and also mapped to significant functional differences on the BBB ($P=0.0002$). This data-drill down revealed that blood pressure spikes at the time of SCI significantly differed between high and low locomotor recovery subgroups (KS = 0.7, $P=0.03$), suggesting that subjects with poorer outcome may have had hypertensive mean arterial pressure (MAP) at the time of injury.

Cross-validation and confirmation of hypertension hypothesis. The data-driven discovery of hypertension as a major predictor of SCI recovery from semi-structured big-data could potentially represent a 'capitalization on chance'[22]. To explicitly rule this out, we performed two waves of additional analyses. First, we independently cross-validated the TDA-based data-driven discovery, by curating an additional data set from subjects with less-severe injuries (12.5 mm) from a separate round of the MASCIS trial (1994–1995, $N=154$) (Fig. 5b) queried from the VISION-SCI repository. Nodes within the network that received thoracic 12.5 mm weight-drop injuries showed distinct subpopulations with significant differences in BBB locomotor recovery (Fig. 5b, circles, $P=0.01$). KS testing of the good versus bad recovery subgroups within this network confirmed that hypertensive events (maximum MAP) during surgery predicted lower locomotor recovery in the chronic phase (KS = 0.6, $P=0.0009$).

Second, we explicitly tested the formal hypothesis that perioperative hypertension predicts long-term outcome using a repeated measures general linear model (GLM) on the 1996 and the 1994–1995 data sets. Explicit hypothesis testing separately confirmed the hypothesis that perioperative MAP (covariate) predicted poorer functional recovery of BBB (dependent) between 1 and 6 weeks post injury (repeated measure). In both data sets, post-injury MAP (15 min after SCI) significantly predicted the main effect of recovery of BBB locomotion following injury (1996, $F(5,20)=3.701$, $P=0.02$; 1994–1995, $F(5,110)=2.671$, $P=0.03$).

TDA-based data-driven discovery versus traditional tools. The fact that TDA-guided discovery uncovered a novel finding that was hiding in plain sight in 20-year-old data, provides strong potential support for this approach. However, we wondered whether a similar set of results could have been revealed using traditional analytics. To test this, we pooled all data from MASCIS ($N=334$) in the VISION-SCI repository and performed side-by-side bivariate correlational analysis and TDA (Fig. 6). Pearson correlation confirmation of the significant inverse correlation between elevated perioperative blood pressure and BBB functional recovery was performed by plotting a bivariate correlation matrix for MASCIS OSU trial subjects ($N=334$) for all measures of survival, histology, perioperative vitals and blood gases, functional recovery, bladder health and weight over 1–6 weeks post SCI (Fig. 6a). Blood pressure measures showing the most significant inverse correlations to BBB recovery were confirmed, with elevated diastolic blood pressure at the time of injury, showing the most significant negative correlations at multiple

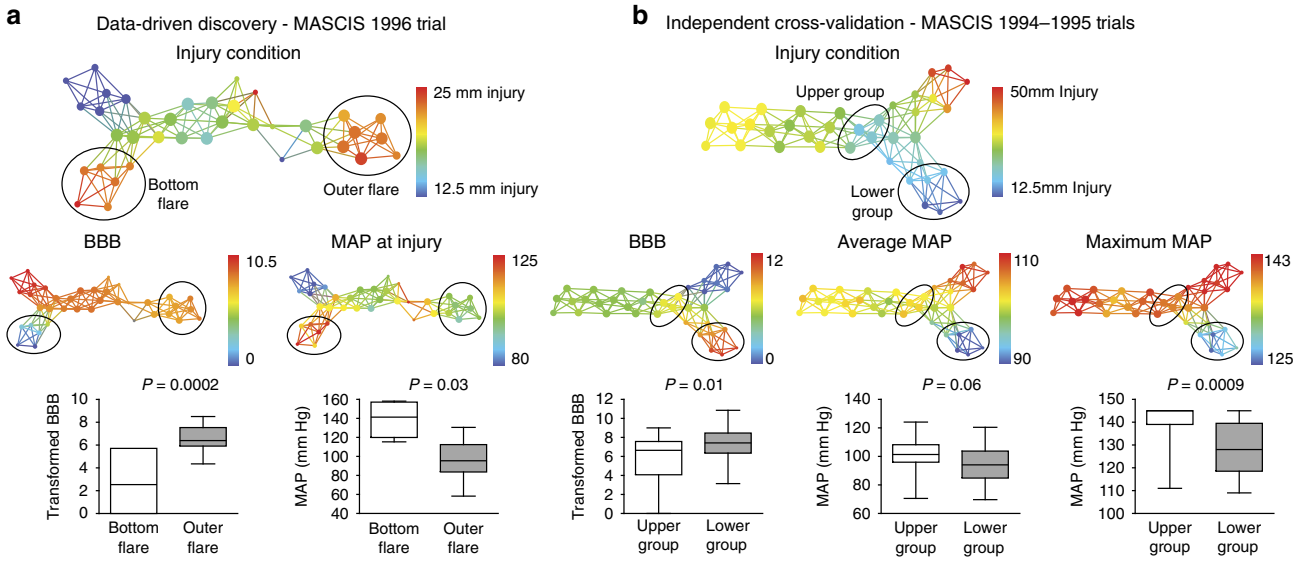

Figure 5 | Perioperative hypertension predicts worse recovery after thoracic SCI. (**a**) Exploration of the TDA network from the MASCIS OSU 1996 methylprednisolone trial ($N=72$) revealed a cluster of subjects in the network given the same targeted injury (circled bottom and outer flares) that showed very significant differences in BBB function ($P=0.0002$). A query of variables with significant differences based on KS test results between these two groups uncovered subjects with significant hypertension during SCI surgery ($P=0.03$) clustering in the groups with poorer functional recovery. (**b**) Cross-validation of these relationships between perioperative blood pressure and functional recovery was performed in a separate group of test subjects from the same 3-year drug trial (MASCIS 1994–1995, $N=154$) with matching outcome measures and subject grouping. Visually guided identification of subjects in the network given the same injury condition (circled upper and lower groups) but showing poorer functional recovery on the BBB scale ($P=0.01$) uncovered the same significant detrimental effect of hypertension during SCI surgery on recovery ($P=0.06$), specifically when assessing peak MAP values recorded during surgery ($P=0.0009$). Box and whisker plots show mean and minimum/maximum range of values. *P* values obtained using student *t*-test for significant differences between groups.

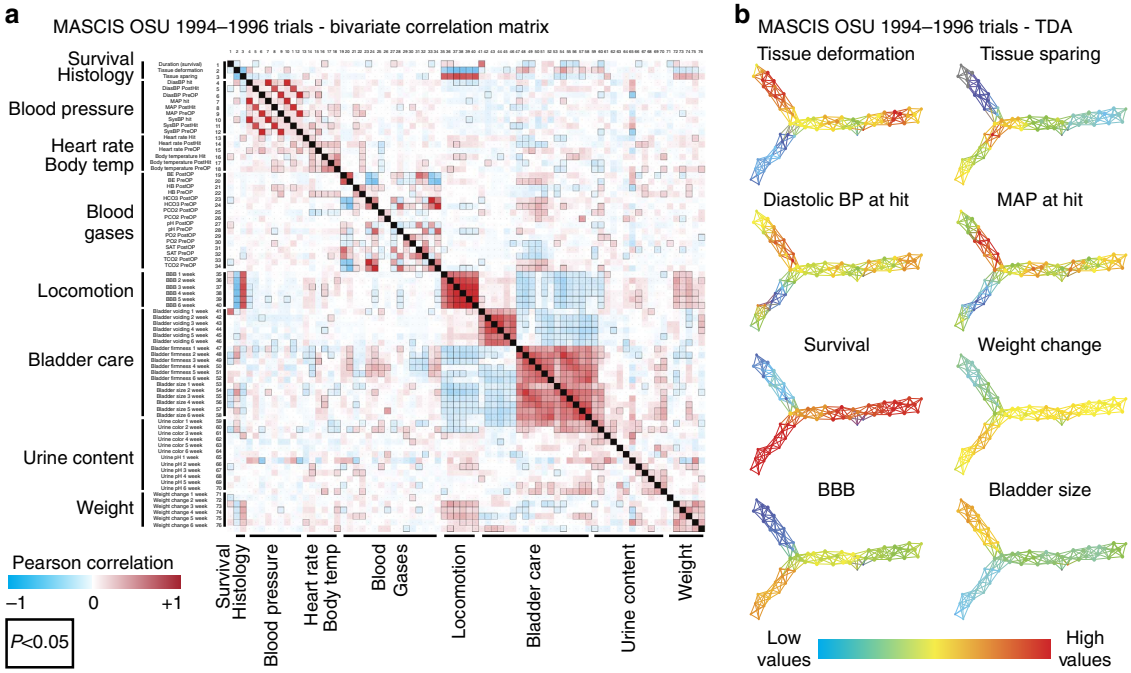

Figure 6 | Comparing traditional tools to TDA in MASCIS data set. (**a**) A bivariate correlation matrix was generated for every outcome measured over time along with measures of heart rate, blood pressure and blood gases before, during and after surgery. Each variable is correlated to every other variable, with clusters of similar measures represented with larger text, with specifics about each measure and collected as the same times post injury (1–6 weeks post injury). Histology includes tissue deformation and tissue sparing. Blood pressure includes diastolic pressure, mean arterial pressure and systolic pressure at time of hit, 15 min after hit (PostHit) and 15 min before hit (PreOP). Similar time bins were collected for heart rate and body temperature. Blood gases were measured only either before (PreOP) or after (PostOP) injury. Locomotion was measured between 1 and 6 weeks using the BBB scale. Bladder function was monitored daily and binned across each week post injury for bladder voiding/expression, firmness, size and urine content was recorded for colour and pH. Weight change between each week post injury was also recorded to assess health. Numbers along the *y*-axis are reflected in the *x*-axis to line up variable comparisons. The heat map represents either negative (blue) or positive correlations between each variable within the matrix, with significant correlations ($P<0.05$) highlighted with black boxes. Although this method of visualizing correlations is useful for understanding how different measures all relate to each other within the context of all other comparisons, it does not allow for mapping of each test subjects placement within the network based on all these complex relationships. (**b**) TDA of the same data set reveals the distribution of every subject within the network, from all subjects in the entire OSU MASCIS trial (1994–1996, $N=334$). TDA revealed the same visually guided relationships between perioperative blood pressure and autonomic and locomotor dysfunction following SCI identified in Fig. 5. Complete mapping of all outcomes and perioperative measures of vitals and blood gases over time were exported into an HTML viewer (Supplementary Software 4).

time points (3–6 weeks), with MAP and systolic blood pressure only showing a significant correlation to BBB deficits at 5 weeks post injury. Additional measures also showed significant correlations to BBB recovery in this large correlation matrix, including expected ones such as tissue pathology, bladder care complications and weight gain, with additional measures of body temperature and several blood gas measures during surgery (bicarbonate; blood pH; total carbon dioxide; and partial pressure of carbon dioxide) also showing significant correlations to BBB. Taken together, we found that the major changes in MAP predicting long-term motor impairment, typically occurring in the range between 100 and 143 mm Hg for upwards of 5 min at a time, occurred immediately post injury, during surgery and in the recovery phase in the animal neuroICU.

Although visualization and interpretation of the complex interactions between all the variables in this data set can, in theory, be achieved by simple correlation, this approach does not identify clusters of subjects that are most sensitive to these interactions across the full spectrum of variables. Navigating the same data set with TDA creates a syndromic map of all subjects based on the full network of correlations, enabling rapid comparative hypothesis testing about factors such as injury condition, recovery rate, autonomic factors or even gender differences (Fig. 6b, Supplementary Software 4, dropdown). All outcomes measured over time, including BBB locomotion, bladder function, weight, and perioperative blood pressure and blood gases were mapped onto the network for each time point (Supplementary Software 4, dropdown). Additional mapping of enrichment for gender differences in the network revealed that subjects within the nodes that showed the strongest relationship between perioperative hypertension and BBB recovery were mostly males. Due to bladder complications being more pronounced in males following SCI[14], and the strong correlation between bladder function and health and recovery of locomotion, males may be more sensitive to the complications of hypertension during surgery, potentially contributing to more autonomic complications post injury, leading to increased morbidity. This TDA-based hypothesis discovery has served to accelerate ongoing interests in our centre in linked preclinical experimental and prospective clinical observational trials of critical care variables including MAP and the use of pressors[23,24] to assess the impact of hypertension, as well as hypotension on recovery of function after SCI.

Discussion

We report the novel application of TDA to extract the fundamental shape of the multidimensional syndromic space

after CNS damage, using preclinical TBI and SCI data as illustrating examples. TDA-based data-driven analyses revealed a set of important findings, some of which dramatically confirmed existing 'hunches' in the published literature, whereas others represented novel findings that were not previously identified, even in legacy data sets (for example, 20-year-old MASCIS studies). As an illustration of value for confirmatory analysis, TDA revealed a dramatic interaction between SCI and concurrent TBI that depended on anatomical location of brain lesions. Although this effect has previously been reported, it only reached significance on a subset of univariate endpoints[15], whereas TDA revealed this effect to be very large and robust at the network level. As an illustration of value for exploratory hypothesis generation, TDA identified potential detrimental consequences of MP treatment on tissue pathology in cervical SCI, and to a lesser extent in thoracic SCI. In attempting to cross-validate this observation, we discovered a novel previously unrecognized relationship between perioperative hypertension and poorer long-term functional recovery. The relationship between perioperative hypotension (<85 mm Hg MAP) and poorer neurological recovery was recently reported in humans with SCI[23], providing a basis for clinical relevance in early neurocritical care on outcomes. However the relationship between acute hypertension has not been reported. Further investigation in humans with SCI needs to be conducted to determine if the findings presented in the current study translate into humans. While the practice guidelines for treatment of acute SCI include avoidance of hypotension, there is little experimental data to support this, and the role of hypertension in outcomes has received less attention[23,25,26]. The findings presented here suggest that both extremes in MAP may contribute to increased morbidity following injury. Additional prospective experiments are currently underway in rats to test the mechanism by which hypertension exacerbates functional deficits following SCI. Based on the literature, the leading mechanistic candidates include increased oedema cord[27], increased hemorrhage[28], blood–brain-barrier breakdown and influx of inflammatory cells and cytokines around the injury. Such effects may promote a more cytotoxic spinal cord micro-environment contributing to increased morbidity[25,29–35]. Taken together with the increased autonomic complications that exist in patients following SCI[36] (for example, autonomic dysreflexia), which may be triggered by haemodynamic events, hypertension during acute management of SCI may pose a significant risk for patients. This suggests that careful monitoring of blood pressure in acute patients may need to be considered for both the upper (hypertension) and lower limits (hypotension), as both extremes may impact neurological recovery.

The present application of a big-data-analytic tool for novel discovery has broad implications for translational SCI research. Previous work has demonstrated both the univariate and multivariate impact of graded cervical SCI[13] in rats and primates[14,16], as well as a univariate assessment of a combined SCI and TBI preclinical model in rats[15]. The results of prior studies show that information about impairment of function and tissue pathology can be understood at the univariate level, and to a greater degree at the multivariate level, providing powerful opportunities for therapeutic discovery that harnesses CNS trauma big-data in ensemble. However, progress is hampered by the intensive data pre-processing typically required before and after analysis to generate a full view of the multidimensional syndromic state in CNS injury[37]. The difficulty of sophisticated analytics may partially account for the slow progress to both understand and successfully treat these complicated CNS injury syndromes. Typical CNS injury studies generate enormous quantities of data, yet only a few of these measures are assessed at a time. The ability to interpret the full pattern of disease pathology and recovery is further confounded by basic visualization attempts using bar graphs and/or recovery curves combined with potentially inappropriate statistical techniques to detect significant effects[38] in a manner that is at once both prone to false-positives (familywise type-1 error) and wasteful of information (multivariate type-2 error)[39]. Taken together, these factors may hinder progress to rapidly translate promising preclinical studies into clinical trials, and may point researchers in the wrong direction regarding the conclusions that can be drawn from their studies.

TDA applies the mathematical concepts from geometric topology to unlock relationships in data that would be considered as noise by traditional parametric approaches such as regression and GLMs[40]. By extracting the fundamental shape from the entire multidimensional data set, TDA ascribes meaning to an otherwise unforeseen pattern of relationships among individuals. The TDA algorithm achieves this goal by iterating through multiple views of lower dimensional shape of the data to extract the persistent shape of the syndromic space across these multiple views using ensemble machine learning. Through this process, TDA can resolve meaningful signal from 'noise' by identifying its true source, improving our understanding of the whole data set. TDA has been used previously to navigate complicated, high-dimensional biological data sets including functional brain connectivity[41,42] and biomolecular folding pathways[43]. Novel applications for TDA in precision medicine are also beginning to appear in the literature. For example, TDA has been used to uncover novel relationships in immune cell reactivity between patients with type-1 and type-2 diabetes[44], and in identifying novel subgroups of patients with asthma and the unique relationships of specific T-cell mediated interleukins with these patient subgroups[45]. Another prominent example of TDA's application towards precision medicine was found in breast cancer data regarding genetic influences on patient survival that had not been previously identified, even-though the data sets containing this information had been publically available for over 10 years[46]. Similar methods can now be applied for neurotrauma data sets at both the preclinical and clinical level, given the emergence of large-scale multicentre repositories targeting precision medicine for the CNS[11,37].

In the present paper, we expand the concepts of precision medicine to the application of TDA for preclinical translational discovery, using CNS injury data sets containing diverse information from multiple preclinical treatment trials with histopathological, functional and health outcomes. TDA allows for both rapid analysis and rapid visualization of all measures collected in a particular study to increase efficiency of recovery testing following injury, and allows drill down into subpopulation clusters for targeted hypothesis testing regarding treatment efficacy across the complex variability that exists in SCI. Due to the high dimensionality of many SCI and TBI data sets, it can be difficult to interpret which measures are sensitive to improved recovery in therapeutic trials, and whether particular subgroups are selectively responsive. As shown in the present paper, the network generated from TDA can then be harnessed to test the generality of therapies—that is, whether treatments are effective within the full syndromic space—as well as specific therapeutic features such as determining whether particular outcome measures are more sensitive to therapeutic targeting.

It should be noted that the current work does have limitations. Perhaps the most translationally significant finding was the identification of a detrimental relationship between perioperative hypertension and long-term locomotor recovery following SCI. It is unclear from mining the animal hospital records what specific mechanisms may lead to animals having hypertensive episodes

during SCI operation and recovery. One potential confounder is that variability in anesthesia may impact blood pressure. Although it is difficult to completely discount this possibility in a retrospective study, there is no evidence of systematic variability in anesthesia reflected in the detailed perioperative animal care records. In addition, the MASCIS pilot study tested multiple anesthetics and developed a rigid protocol of pentobarbital anesthesia, with the contusion injury delivered at a standardized time point of 1 h, with surgical plane confirmed by areflexia for the multicentre study data presented here. However, further experimental studies are needed to assess the impact of anesthetics as a potential mediator of the perioperative hypertension–locomotion relationship[47]. Regarding the potential for TDA as a precision medicine tool applied to SCI and TBI research, the current study was performed in inbred animals with consistent graded injuries living in optimal conditions that were tightly controlled within a given study (but highly variable across centres and strain). This intrinsic multicentre variability is useful for providing a proof-of-concept validation of TDA for neurotrauma in the face of potential cross-laboratory variance. However, it remains an open question whether TDA could overcome high variability seen in human clinical data for SCI and TBI, though previous studies using TDA in other diseases demonstrate its value for clinical decision support[44–46].

In conclusion, rapid visualization and analysis of CNS injury big-data may facilitate rapid, accurate big-data analysis of preclinical and clinical studies, allowing for quicker validation of hypotheses tested. By exploring a large preclinical data set with multiple injury models, outcome measures and study designs, TDA discovered unique features of TBI + SCI determined by injury location, and detrimental influences of perioperative hypertension on locomotor recovery and bladder function that were previously unpublished. In this sense, TDA presents a powerful and novel bioinformatics tool for the field of neurotrauma research for testing large, heterogeneous data sets. By mapping all data collected across an entire test subject population as a multidimensional topology, TDA helps extract new knowledge about neurotrauma populations and their associated states of disease and recovery. This may expedite the translational pipeline for therapeutic discovery in neurological disease research.

Methods

Proof-of-concept application of TDA to neurotrauma data sets. TDA was used to rapidly analyse and visualize clustering of individuals based on their similarity across hundreds of variables simultaneously (Fig. 1). TDA is an adaptation of the methods of topology, the mathematical discipline which studies robust methods of measuring and representing shape, to create compact visual representations of high-dimensional data sets[40,48]. This is performed automatically within the software, by deploying an ensemble machine learning algorithm that iterates through overlapping subject bins of different sizes that resample the metric space (with replacement), thereby using a combination of the metric location and similarity of subjects in the network topology. After performing millions of iterations, the algorithm returns the most stable, consensus vote for the resulting 'golden network' (Reeb graph), representing the multidimensional data shape[12,40]. The application of this method to our data sets creates clusters of subjects which appear as nodes (points) and relations among clusters are represented as interconnections ('edges' or lines) between the nodes (Fig. 1d). Once the topological network is developed, rapid exploration of the full neurotrauma syndrome and its various manifestations across different measures can be performed (Supplementary Software 1–4). Although the application of a licensed version of TDA software was used for the present study through the Ayasdi cloud-based platform (www.ayasdi.com, v 2.0), open source versions of the program code are available in either Python[48] or R[49,50].

TDA applied to combined TBI and cervical SCI in rats. We applied TDA to a data set containing several controlled models for combined TBI and SCI in 2–3-month-old female Long Evans rats ($n = 49$, $P = 94$) from a previously published study[15]. Data were analysed using the variance-normalized Euclidean metric (VNE), which finds the mean and s.d., and rescales the value of the coordinate around its mean by dividing by the s.d. of the set of values taken by the coordinate. This metric calculates the distance between two points, taking into account that each column in the data set could have significantly different variance. VNE distance between two points X and Y is given by:

$$\mathrm{VNE}(X,\ Y) = \sqrt{\sum_{i=1}^{N} \frac{(X_i - Y_i)^2}{V_i}} \quad (1)$$

Where V_i is the variance associated with each column i and is given by:

$$V_i = \frac{1}{M}\sum_{j=1}^{M}\left(Z_{j,i} - \bar{Z}_i\right)^2 \quad (2)$$

And $\bar{Z}_i$ is the mean of column i and is given by:

$$\bar{Z}_i = \frac{1}{M}\sum_{j}^{M} Z_{j,i} \quad (3)$$

VNE was combined with the principal and secondary metric SVD lenses, which are analogous to PCA. The network was set at a resolution of 30 and a gain of $\times 4.0$ (equalized) from which subjects with shared syndromic features were clustered together and distributed into a syndromic network topology (Fig. 2). Adjusting the resolution and gain alters the number of bins and the degree of overlap of these bins. Once the network is extracted, resolution and gain are used to 'focus' the network similar to focusing a microscope on an image. We begin with a standard resolution of 30 and gain of 4.0 and then adjust these parameters to ensure that the majority of subjects are included in a connected node (as opposed to isolated from the network), and that all nodes are connected as a single network (if possible). Changing the resolution and gain alters the number of bins and the degree of overlap of these bins respectively, spreading subjects out across more nodes (high resolution) or forcing more subjects into each node (high gain). Network extraction, 'focusing' and face validation of the syndromic space is based solely on primary outcomes of interest (for example, locomotion), while remaining blind to experimental conditions/predictors. In this sense we begin with the full outcome pattern and then reverse engineer the largest predictors in a data-driven manner.

Variables that were analysed included all available endpoint data, excluding predictor data such as categorical injury condition, gender or treatment. For networks in Figs 1–3, these endpoint data included injury biomechanics of brain and spinal cord tissue displacement, force and velocity, terminal tissue sparing, weight change, and 6-week time-course data points for measures of grooming, paw preference in the cylinder[13,51], the Basso Beattie Bresnahan (BBB) hindlimb locomotor scale[13,17], the Martinez scale of forelimb locomotion[52] and the Irvine Beattie's Bresnahan (IBB) scale for object manipulation[53,54]. The majority of these variables are conceptualized and listed in Fig. 2a,c, and in the drop-down menu in the living figure Supplementary Software 1. Topologies were colour coded for each injury group,PC1 and PC2 distributions, histopathology and a few key examples of averages over time of functional outcomes (grooming, paw preference, object manipulation, forelimb and hindlimb open field). These were exported from the cloud into an HTML viewer to rapidly visualize and interpret the relationship of functional recovery to injury group and tissue pathology (Supplementary Software 1). For visualized distribution of injury models (Fig. 2c), red nodes indicated a pure population for each particular category, which included uninjured sham controls ($n = 9$), mild TBI ($n = 10$), unilateral 75 kdyn force-driven contusions ($n = 10$), mild TBI contralateral to 75 kdyn force-driven contusion ($n = 10$, SCI + TBI Contra) and mild TBI ipsilateral to 75 kdyn force-driven contusion ($n = 10$, SCI + TBI Ipsi). Schematic diagrams of each injury model illustrate the placement of each injury (black ellipses) or sham controls (open ellipses) to demonstrate the laterality of each injury model that was tested.

Schematic diagrams for measures of functional recovery (Fig. 2a) and histopathology (Fig. 2b) were created for animal model visualization. Terminal outcomes were then visualized at the univariate level (Fig. 2a,b), which is the current standard in the SCI preclinical literature, showing the distribution of subjects for each injury group (Fig. 2c) for grooming, preference for the uninjured forepaw during vertical exploration in a Plexiglas cylinder, and forelimb and hindlimb locomotion in the open field (Fig. 2a). Histological measures of tissue in the brain and spinal cord, and MN sparing along the rostro-caudal extent of the injury were also plotted in the same manner (Fig. 2b).

TDA applied to graded unilateral cervical SCI in rats. We applied TDA to graded unilateral cervical SCI in 2–3-month-old female Long Evans rats ($n = 132$ subjects, $P = 119$ variables, Fig. 3; Supplementary Software 2) from previously published studies[13,51]. Data were analysed using the norm correlation metric equation—equation (4). This metric normalizes the columns to become comparable. This metric is used when the data columns have ranges and means that vary significantly. The norm correlation (Corr) distance between two points is given by the Pearson correlation and is given by $\mathrm{Corr}\ (X,\ Y) = 1 - \mathrm{r}(X',\ Y')$, where X', Y' are the column-wise, mean-centred and variance-normalized versions of X

and Y.

$$r(X,Y)=\frac{N\sum_{i=1}^{N}X_iY_i-\sum_{i=1}^{N}X_i\sum_{i=1}^{N}Y_i}{\sqrt{N\sum_i X_i^2-\left(\sum_i X_i\right)^2}\sqrt{N\sum_i Y_i^2-\left(\sum_i Y_i\right)^2}} \quad (4)$$

This was combined with the principal and secondary metric SVD lenses. These lenses generate a factorization of the data matrix into linearly uncorrelated components. The principal SVD lens is the highest variance component and the secondary SVD is the second highest variance component. These lenses assume that your data is using the Euclidean metric.

$$f(X)=\min_{Z}\sum_{i,j}\left(d(X_i,X_j)-L_2(Z_i,Z_j)\right)^2 \quad (5)$$

The analysis was set at a resolution of 50 and a gain of 5.0 × (equalized) from which subjects with shared syndromic features were clustered together and distributed into the syndromic network topology (Fig. 3; Supplementary Software 2, dropdown).

Variables that were analysed included all endpoint data, excluding predictor information about categorical injury condition, gender or treatment. Endpoint data used for Figs 3–5 include a standardized measure of tissue compression for injury biomechanics across different contusion devices, terminal tissue pathology measured by lesion size and white/grey matter and MN sparing, and 6-week time-course data points for measures of daily or weekly weight change, CatWalk[55], grooming, paw preference in the cylinder[13,51], BBB hindlimb locomotion[17,56], a 4-point measure of forelimb locomotion[13] and the IBB scale for object manipulation[53,54]. Topologies were colour coded for each injury model, PC1 and PC2 distributions, histopathology and a few key examples of functional outcomes (grooming, paw preference, forelimb and hindlimb open field) at 7, 21 and 42 DPL. These were exported from the cloud into an HTML viewer to monitor recovery of each outcome over time in relation to injury model and tissue pathology (Supplementary Software 2, dropdown). Heat maps for the colour schemes of the flares represent the range of highest values (red) to lowest values (blue) for each respective outcome being visualized (for example, lesion size; blue = 0%, red = 100% lesion, Fig. 3b). For visualized distribution of injury models, red nodes indicated a pure population for each particular category of graded SCI, which included uninjured sham controls ($n=16$), hemisections ($n=9$), 75 kdyn ($n=31$) and 100 kdyn ($n=34$) unilateral contusions with the force-driven impactor, and 6.25 mm ($n=10$) and 12.5 mm ($n=32$) unilateral contusions with the weight-drop impactor (Fig. 3; Supplementary Software 2, dropdown).

A detailed interpretation of the syndromic space for graded unilateral cervical SCI has been reported previously[13], however, those analyses were performed in SPSS v. 19, and do not allow for rapid analysis and visualization of the syndromic SCI space that is presented here.

Data-driven exploration of preclinical drug trial efficacy. Comparison of continuous variables was performed by two tests: KS test and t-test. The KS test was used to investigate the non-parametric probabilistic distributions of samples across each (one-dimensional) variable, while the t-test explores whether the null hypothesis (mean value of both samples) is supported. Comparison of categorical variables was performed by Fisher exact test. These methods were used to identify group differences from the graded cervical SCI data set between selected nodes that were classified based on a combination of purity for both injury condition (for example, 12 mm weight-drop) and treatment condition (for example, MP, minocycline, No drug; Fig. 3d, red nodes). Nodes satisfying both these criteria were designated as groups and analysed for measures that differentiated the groups from each other. Significant differences between these groups were based on KS scores with the largest absolute values (0.75–1.0) and KS P values.

Data-driven exploration of MASCIS as a cross-validation test. Data mined from the VISION-SCI repository[14] for previous trials of MP in SCI resulted in identification of the MASCIS preclinical trial from the OSU testing site. This was an NIH-sponsored multicentre trial (1994–1997) to validate the contusion model for SCI using the weight-drop contusion device[19], and to test the efficacy of pharmacological treatments for SCI. Only subjects from year 3 (1996, $N=72$) had un-blinded treatment codes in the current version of the database. A norm correlation metric and L-infinity Centrality lens (resolution 30, Gain 4.0 ×, equalized) was used to generate the network from 2–3-month-old rats receiving graded thoracic (T9) bilateral contusions (12.5 and 25 mm injuries, in both males and females, across 6 MP combination treatment conditions) with 49 separate outcome measures. Only endpoint data were used in the analysis, excluding predictor information about categorical injury condition, gender or treatment. Endpoint data used in the analysis included tissue deformation injury biomechanics and vitals measured during the SCI operation, including body temperature, heart rate and blood pressure (systolic, diastolic, mean). Vitals, along with blood gases, were measured using an intra-arterial tail catheter, and averages and maximum values were taken from 15 min before injury (PreOP), at the time of injury and 15 min post injury (PostOP). Post injury functional outcomes included averages for recovery of bladder function, urine content, weight gain and locomotor recovery on the BBB scale during the 6-week time period prior to sacrifice and terminal total tissue sparing. The full list of these variables is provided in Fig. 6b and the drop-down menu of Supplementary Software 4. These data were analysed using L-infinity centrality, which groups subjects into nodes in the network using the maximal distance of each subject from all other subjects.

$$f(x)=\max_{Y}d(X,Y) \quad (6)$$

Only subjects in the vehicle ($N=10$) and MP ($N=12$) treated groups had complete data for BBB locomotion and tissue sparing for hypothesis testing about treatment effects (Fig. 4).

Testing perioperative hypertension-recovery association. KS tests were used to compare group differences in the networks generated for the MASCIS OSU trial year 3 data set ($N=72$) to identify significant group differences between BBB functional recovery that were predicted by MAP levels at the time of injury (Fig. 5a). Rats with an age range of 2–5 months from years 1–2 of the MASCIS trial (1994–1995, $N=154$) with the same 49 outcome measures were analysed using the same TDA parameters as the 1996 data set to validate the hypothesis that elevated MAP during SCI surgery significantly predicted poorer functional recovery (Fig. 5b). Confirmation of perioperative MAP levels predicting poorer neurological recovery was performed in SPSS v. 19 using a GLM repeated measures ANOVA. The dependent variable was BBB locomotor score, time points of 1–6 weeks post injury were the repeated measures, and MAP values at either PreOP, PostOP, or at the time of injury were each used separately as covariates within the GLM and tested on each data set separately (1996 and 1994–1995). The bivariate correlation matrix comparing all variables measured over time in the entire MASCIS OSU trial ($N=334$) was generated in SPSS v.19, and two versions were overlaid to depict both Pearson correlation values and valence (Fig. 6a, red–blue heat map for positive or negative correlations, respectively), and the significance of each correlation (outlined boxes). Comparison of the bivariate correlation matrix to TDA on the same data set and set of variables measured over 6 weeks post SCI ($N=334$, $P=150$; TDA metric = norm correlation, L-infinity centrality lens, resolution 50, Gain 4.0 ×, equalized) was plotted together to assess the greater efficacy of TDA to perform visually guided comparisons of the networked interactions between all test subjects based on correlations of outcome variables for a more comprehensive, holistic view and exploration of the SCI syndrome (Fig. 6b, Supplementary Software 4, dropdown).

Statistical analysis. Statistical analysis testing between groups for the identified measures were performed in Ayasdi v2.0 for group differences in the network, and plotted for box plots or histograms in GraphPad Prism 5 and analysed for significance using two-tailed t-tests and one-way ANOVAs in SPSS v19 (Figs 3–5).

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Acknowledgements

This work was funded by the Craig H. Neilsen Foundation Grant 224308, the National Institutes of Health (NIH) NS067092 (A.R.F.), NS069537 (A.R.F), NS038079 (J.C.B. and M.S.B.), NS031193 and AG032518 (M.S.B. and J.C.B.), NS079030 (J.L.N.), NS032000 (W.Y.; M.S.B. site PI, multicentre study); NYSCoRE CO19772 (M.S.B. and J.C.B.), the Department of Defense (DoD) grants W81XWH-10-1-0910 (M.S.B.) and W81XWH-13-1-0297 (M.S.B.), and Wings for Life Foundation grants WFLUS008/12 and WFLUS006/14 (A.R.F.). We thank J.R. Huie and J. Haefeli for useful comments, and A. Lin and S. Visuthikraisee for technical support.

Author contributions

J.L.N. performed all analyses, prepared all figures and drafted the manuscript. J.L.N., J.P. and A.R.F. conceived of the application of TDA to the data sets presented. J.L.N., A.W.L., C.F.G. and A.R.F. all contributed to data wrangling of original data. J.L.N., A.W.L., C.F.G., G.T.M., J.C.B., M.S.B. and A.R.F. all contributed to data provenance in preparation of data visualization with TDA. T.I., K.-A.I., J.C.G., A.C.T., J.C.B. and M.S.B. collected primary experimental data. G.E.C. developed TDA. J.P., J.K., P.Y.L. and G.E.C. worked on the development of the data analytics and visualization software. J.L.N., J.P., J.K. and A.R.F. developed the optimal parameters to apply TDA to the presented data. T.C.P., P.Y.L., G.E.C., M.S.B., J.C.B. and A.R.F. edited the manuscript. G.T.M., W.Y., M.S.B., J.C.B. and A.R.F. were involved in study design and interpretation of the original data sets. J.L.N., J.P., G.T.M., J.C.B., M.S.B. and A.R.F. contributed to the interpretation of the results.

Additional information

Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing financial interests: J.P., J.K., T.C.P, P.Y.L, and G.E.C. are current or former employees of Ayasdi Inc. and own shares of the company. All other authors declare no competing financial interests.

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How to cite this article: Nielson, J. L. *et al.* Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury. *Nat. Commun.* 6:8581 doi: 10.1038/ncomms9581 (2015).

JNS SPINE

CLINICAL ARTICLE

Complications and outcomes of vasopressor usage in acute traumatic central cord syndrome

William J. Readdy, BS,[1] William D. Whetstone, MD,[1,2] Adam R. Ferguson, PhD,[1] Jason F. Talbott, MD, PhD,[1,3] Tomoo Inoue, MD, PhD,[1] Rajiv Saigal, MD, PhD,[1] Jacqueline C. Bresnahan, PhD,[1] Michael S. Beattie, PhD,[1] Jonathan Z. Pan, MD, PhD,[1,4] Geoffrey T. Manley, MD, PhD,[1] and Sanjay S. Dhall, MD[1]

[1]Department of Neurological Surgery, Brain and Spinal Injury Center; and Departments of [2]Emergency Medicine, [3]Radiology and Biomedical Imaging, and [4]Anesthesia, University of California, San Francisco, California

OBJECT The optimal mean arterial pressure (MAP) for spinal cord perfusion after trauma remains unclear. Although there are published data on MAP goals after spinal cord injury (SCI), the specific blood pressure management for acute traumatic central cord syndrome (ATCCS) and the implications of these interventions have yet to be elucidated. Additionally, the complications of specific vasopressors have not been fully explored in this injury condition.

METHODS The present study is a retrospective cohort analysis of 34 patients with ATCCS who received any vasopressor to maintain blood pressure above predetermined MAP goals at a single Level 1 trauma center. The collected variables were American Spinal Injury Association (ASIA) grades at admission and discharge, administered vasopressor and associated complications, other interventions and complications, and timing of surgery. The relationship between the 2 most common vasopressors—dopamine and phenylephrine—and complications within the cohort as a whole were explored, and again after stratification by age.

RESULTS The mean age of the ATCCS patients was 62 years. Dopamine was the most commonly used primary vasopressor (91% of patients), followed by phenylephrine (65%). Vasopressors were administered to maintain MAP goals for a mean of 101 hours. Neurological status improved by a median of 1 ASIA grade in all patients, regardless of the choice of vasopressor. Sixty-four percent of surgical patients underwent decompression within 24 hours. There was no observed relationship between the timing of surgical intervention and the complication rate. Cardiogenic complications associated with vasopressor usage were notable in 68% of patients who received dopamine and 46% of patients who received phenylephrine. These differences were not statistically significant (OR with dopamine 2.50 [95% CI 0.82–7.78], p = 0.105). However, in the subgroup of patients > 55 years, dopamine produced statistically significant increases in the complication rates when compared with phenylephrine (83% vs 50% for dopamine and phenylephrine, respectively; OR with dopamine 5.0 [95% CI 0.99–25.34], p = 0.044).

CONCLUSIONS Vasopressor usage in ATCCS patients is associated with complication rates that are similar to the reported literature for SCI. Dopamine was associated with a higher risk of complications in patients > 55 years. Given the increased incidence of ATCCS in older populations, determination of MAP goals and vasopressor administration should be carefully considered in these patients. While a randomized control trial on this topic may not be practical, a multiinstitutional prospective study for SCI that includes ATCCS patients as a subpopulation would be useful for examining MAP goals in this population.

http://thejns.org/doi/abs/10.3171/2015.2.SPINE14746

KEY WORDS ATCCS; central cord; traumatic spinal cord injury; cervical spine; spinal cord perfusion; vasopressors; dopamine; trauma

ABBREVIATIONS AANS/CNS = American Association of Neurological Surgeons and Congress of Neurological Surgeons; ASIA = American Spinal Injury Association; ATCCS = acute traumatic central cord syndrome; ICU = intensive care unit; ISP = intraspinal pressure; MAP = mean arterial pressure; SCI = spinal cord injury; SCPP = spinal cord perfusion pressure.

SUBMITTED July 29, 2014. **ACCEPTED** February 5, 2015.
INCLUDE WHEN CITING Published online July 31, 2015; DOI: 10.3171/2015.2.SPINE14746.
DISCLOSURE Dr. Dhall reports receiving speaking honoraria from DePuy and Globus.

Since Schneider colleagues' well-known description of acute traumatic central cord syndrome (ATCCS) in 1954, significant research has focused on the management of these cases.[18] In recent years, there has been an increased focus on ATCCS, as this represents the most common form of incomplete spinal cord injury (SCI).[3] Additionally, ATCCS complications have been shown to increase in elderly patients.[14] As the US population ages, expanding knowledge of ATCCS will only become more important. Given the potentially debilitating nature of these injuries, and their impact on our society, it is important to explore the medical and surgical management of ATCCS.[5]

Many recent studies on SCI and ATCCS have focused on the timing of surgical intervention and decompression and report mixed results, all citing the need for additional prospective studies.[19,24,26] These studies, along with recent prospective investigations, suggest that early surgical intervention (decompression within 24 hours of SCI) may improve long-term prognosis.[2,9,24] While the focus on surgical decompression, efficacy, and timing is an important aspect of ATCCS management, little focus has been placed on medical management and perfusion for these patients.[2]

As part of the medical management of SCI, there has been an increased focus on vasopressor utilization. Previous studies have linked vasopressor support to improved outcomes, but recognized that there are no validated protocols for the implementation of these interventions.[15,21] The 2013 American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS) guidelines for cervical SCI treatment recommended raising the mean arterial blood pressure of acute SCI patients to the range of 85–90 mm Hg, while acknowledging that further research should be conducted to formulate consistent guidelines and protocols.[2,17] As this recommendation was made primarily based on a single, large, retrospective study with significant positive results, the AANS/CNS author group encouraged more robust research as it relates to the medical management of cervical SCI subpopulations.

Concurrently with ongoing research investigating vasopressor utilization for traumatic SCI, poor clinical outcomes have been reported in the setting of early vasopressor use for critically injured, nonneurosurgical, trauma patients.[16] Excluding traumatic brain injury and SCI, Plurad et al. found a significant, fluid status–independent association between early vasopressor administration and mortality.[16] In the setting of septic shock and cardiogenic shock, other studies found that dopamine was associated with significantly higher complication rates and mortality when compared with norepinephrine.[6,7] To the best of our knowledge, no previous studies have evaluated the role and potential risks of vasopressor utilization specifically in ATCCS patients. Due to the frequency of ATCCS, and its increased incidence in the aging population, research related to the medical management of these patients has become increasingly important, particularly in light of the current lack of universal standards.[2,3,14,17] In this study, we explored the ATCCS subpopulation of acute SCI in order to establish a better understanding of perfusion pressure management in an effort to complement ongoing research related to surgical timing and decompression, and to provide a detailed analysis of complications in these injuries.[9] Additionally, we hypothesized that specific vasopressors may be linked to higher complication rates, along the lines of recent research on critical trauma and shock.[6,7,12]

Methods

This study was reviewed and approved by the Committee on Human Research at the University of California, San Francisco, with an exemption from individual patient consent. We performed this retrospective cohort study of patients at a single Level 1 trauma center and created a database for analysis in REDCap (Research Electronic Data Capture), which was hosted at the University of California, San Francisco, in order to maintain data security and validity.

Population Selection

Potential study participants were identified by querying a preexisting database maintained by the Department of Neurological Surgery, which included all sequential patients with a principal diagnosis of SCI (ICD code: 953–957) from 2005–2011. This database includes 131 patients who met the following criteria: 1) age ≥ 18 years; 2) presence of SCI; 3) admission to the intensive care unit (ICU); and 4) received vasopressors to meet mean arterial pressure (MAP) goals for greater than 24 hours. For this study, we had the specific additional inclusion criteria of the presence of central cord syndrome, as defined by the 2013 AANS/CNS guidelines for the management of ATCCS.[2] From this subpopulation, an additional comprehensive chart review was conducted to elucidate a better understanding of the injury and its management.

Population Characteristics, Complications, and Outcomes

The following variables were collected from the Department of Neurological Surgery database: sex, age, year of injury, vasopressor administration (type and duration of administration), American Spinal Injury Association (ASIA) grade on admission and discharge, level of SCI, and characteristics of injury. These data were then expanded by a blinded researcher by adding variables, including trauma characteristics, administration of methylprednisolone or other steroids, hospital length of stay, ICU length of stay, and surgical interventions. These data were collected from all aspects of the chart, including discharge summaries, nursing notes, progress notes, consent for procedures, operative reports, rehabilitation notes, and pharmacy records. The blinded researcher also independently verified the original data obtained from the departmental database.

Another researcher also reviewed the complications. These included surgical infections, wound complications, hospital-acquired infections, respiratory failure, hemodynamic complications, and cardiogenic complications. Cardiogenic complications included elevated troponins, atrial fibrillation, ventricular tachycardia, significant tachycardia (heart rate > 130 bpm), and significant bradycardia (heart rate < 50 bpm). Additionally, invasive procedures—including intubation, tracheostomies, gastrostomies, arterial

line placement, central line placement, and peripherally inserted central catheters—were reviewed as indicative of advanced medical care. Outcomes were determined based on improvement in neurological function, as indicated by the ASIA grade from admission to discharge and/or death. ASIA grade was selected as the measure of neurological function, given the recommendations of the AANS/CNS guidelines for the classification of cervical injuries and significant validation for the prognostic value of the ASIA grade.[10,13,25]

Statistical Analysis

Descriptive statistics were used to examine the complications associated with vasopressor administration in ATCCS patients. All statistical analyses were performed using SPSS statistical analysis software (IBM SPSS Statistics for Macintosh, version 22.0). For all univariate analyses, the continuous variables are presented as the means with corresponding standard deviations. The univariate descriptions of the categorical data are presented as the incidence and associated percentages. Complications associated with the administration of the 2 primary vasopressors—dopamine and phenylephrine—were compared utilizing the chi-square and Fisher exact tests. Given the high incidence of ATCCS in older patients, an additional subanalysis was performed between patients older and younger than 55 years, which is an age cutoff point based on the recent literature on vasopressors.[16] These groups were further compared using the Pearson chi-square test for dichotomous variables and 2-tailed t-tests for continuous data. For all statistical comparisons, statistical significance was defined as $p \leq 0.05$. The odds ratios were calculated for all cross-tabulated descriptive statistics with accompanying 95% confidence intervals.

Results

Cohort Description and Management

Of the 131 patients in the original database, 34 were determined to have ATCCS, as defined by the inclusion criteria, with complete records available for analysis. As shown in Table 1, 28 (82%) were male and 6 (18%) were female with a mean age of 61.53 ± 16.33 years. The average hospital length of stay was 18.64 ± 19.09 days with an average of 11.67 ± 13.73 days of care in the ICU. The acute SCI methylprednisolone protocol was administered to 20 patients (59%), while 14 patients (41%) were determined to be ineligible for the steroid protocol based on the decisions of their managing surgeon. Chart review indicated that methylprednisolone was not administered for multiple reasons, including medical comorbidities, injury severity, surgeon preference, and timing outside of the initial window of therapeutic intervention. Patients who did not receive steroids presented with more severe injury when compared with the group that received steroids, as indicated by higher average Injury Severity Scores (28 vs 21, respectively), but this did not reach significance ($p = 0.353$). There was no statistical difference in cardiogenic complications between patients who received or did not receive steroid protocols (85.0% for patients who received steroids [17 of 20] vs 64.29% for patients who did not receive steroids [9 of 14]; OR with steroids 3.142 [95% CI 0.608–16.289], $p = 0.161$). Additionally, when comparing the steroid group to the nonsteroid group, there were no statistical differences in any of the measured complication rates or outcomes. Decompressive surgery was performed in the first 24 hours in 16 patients (47%). Surgical intervention after 24 hours was noted in an additional 9 patients (26%), with the remaining 9 patients having no surgical intervention. Those patients who did not have surgical intervention either elected against the procedure, were medically unstable to the extent that the risks outweighed the benefits, or saw improvement without decompression. Of the patients who underwent decompressive surgery, 64% (16 of 25 patients) underwent surgery within the first 24 hours.

TABLE 1. Descriptive demographics*

Variable	Value
No. of patients	34
Male	28 (82.35)
Female	6 (17.65)
Mean age (yrs)	61.53 ± 16.33
Mean MAP goals >85 mm Hg (hrs)	100.78 ± 47.54
Mean ISS	23.52 ± 17.91
Steroids administered	20 (58.82)
No steroids	14 (41.18)
Surgery in <24 hrs	16 (47.06)
Surgery in >24 hrs	9 (26.47)
No surgery	9 (26.47)
ASIA grade improvement	19 (55.88)
No ASIA grade improvement	15 (44.12)
Mean ICU LOS (days)	11.67 ± 13.73
Mean hospital LOS (days)	18.64 ± 19.09
Mortality	2 (5.88)

ISS = Injury Severity Score; LOS = length of stay.
* Continuous variables are reported as the mean ± SD; categorical variables are reported as number (%).

Neurological Outcomes

Table 2 provides a detailed review of the cohort stratified by ASIA grade on admission. At the time of admission, there were 8 ASIA Grade A (24%), 5 Grade B (14%), 8 Grade C (24%), 12 Grade D (35%), and 1 Grade E (3%) patients. Improvement of at least 1 ASIA grade was observed in 19 patients (56%); the remaining 15 patients had the same ASIA grade at admission and discharge. Two patients died during the course of their treatment, resulting in a mortality rate of 6%. One patient suffered from pulseless electrical activity in the field and was resuscitated, but never recovered from other injuries. He was treated aggressively but his Glasgow Coma Scale score never improved above 5T, and the family elected to withdraw care in the context of multiple organ failure. The second death occurred in an elderly patient who fell while standing. The patient developed significant multisystem organ failure that required mechanical ventilation and acute renal replacement therapy. The patient also required reversal of

TABLE 2. Incidence of results stratified by initial ASIA grade*

Variable	ASIA Grade				
	A (n = 8)	B (n = 5)	C (n = 8)	D (n = 12)	E (n = 1)
1-grade improvement	0 (0)	2 (40)	6 (75)	5 (41.67)	0 (0)
2-grade improvement	2 (25)	2 (40)	1 (12.5)	0 (0)	0 (0)
3-grade improvement	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)
No improvement	5 (62.5)	1 (20)	1 (12.5)	7 (58.33)	1 (100)
Dopamine administered	8 (100)	5 (100)	6 (75)	11 (91.67)	1 (100)
Phenylephrine administered	5 (62.5)	4 (80)	4 (50)	9 (75)	0 (0)
Dopamine administered first	6 (75)	4 (80)	6 (75)	10 (83.33)	1 (100)
Phenylephrine administered first	2 (25)	1 (20)	2 (25)	2 (16.67)	1 (100)
Dopamine complications	5/8 (62.5)	4/5 (80)	4/6 (66.67)	7/11 (63.64)	1/1 (100)
Phenylephrine complications	4/5 (80)	2/4 (50)	2/4 (50)	2/9 (22.22)	0/0 (0)
Pneumonia	3 (37.5)	2 (40)	1 (12.5)	0 (0)	0 (0)
Respiratory failure	8 (100)	4 (80)	1 (12.5)	2 (16.67)	0 (0)
Urinary tract infection	3 (37.5)	2 (40)	2 (25)	1 (8.33)	0 (0)
Tracheostomy	3 (37.5)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrostomy	1 (12.5)	0 (0)	0 (0)	1 (8.33)	0 (0)
Steroids administered	5 (62.5)	1 (20)	5 (57.5)	9 (75)	0 (0)
No steroids	3 (37.5)	4 (80)	3 (37.5)	3 25)	1 (100)
Surgery in <24 hrs	4 (50)	3 (60)	3 (37.5)	5 (41.66)	1 (100)
Surgery in >24 hrs	3 (37.5)	2 (40)	3 (37.5)	2 (16.66)	0 (0)
No surgery	1 (12.5)	0 (0)	2 (25)	5 (41.66)	0 (0)
Mean age (yrs)	63.88 ± 15.64	64.40 ± 15.19	63.125 ± 18.11	60.33 ± 15.80	30 ± 0
Mean MAP goals >85 (hrs)	103.5 ± 43.94	149.5 ± 12.37	86.29 ± 51.93	93.583 ± 49.94	72 ± 0
Average ICU LOS (days)	26 ± 22.25	12.8 ± 6.05	6.5 ± 5.10	5.75 ± 2.70	4 ± 0
Average hospital LOS (days)	33.88 ± 25.83	28.6 ± 20.99	12.5 ± 10.80	9.66 ± 9.28	4 ± 0

* Continuous variables are reported as the mean ± SD; categorical data are reported as number (%).

preinjury coagulopathy and suffered from multiple nosocomial infections, which ultimately resulted in his death.

Vasopressor Administration

The characteristics of vasopressor utilization can be found in Table 3. Vasopressors were administered to obtain MAP goals > 85 mm Hg in all patients, for a mean 101 ± 48 hours (4.2 days), before being relaxed to lower goals. This mean time was affected by 2 patients who were transferred to another acute care center for management directly from the ICU while still receiving MAP goals early in their hospitalization. Eighteen patients (53%) had their vasopressor changed due to complications, and 12 patients were concurrently administered 2 or more vasopressors (35%). Dopamine was administered to 31 patients (91%) for MAP goals, and phenylephrine was administered to 22 patients (65%). A detailed delineation of the vasopressor-associated complications can be found in Table 4. For the entire cohort, there was a nonsignificant trend toward a higher complication rate with dopamine (68% of patients who received dopamine experienced complications [21 of 31 patients] vs 45% for phenylephrine [10 of 22 patients]; OR with dopamine 2.52 [95% CI 0.82–7.78], p = 0.105). In the subgroup of patients age > 55 years, dopamine produced statistically significant increases in complications rates when compared with phenylephrine (see Table 5). This effect was not observed in a comparison of dopamine to phenylephrine in the group < 55 years. Further analysis showed that age > 55 years was also associated with all vasopressor complications (90% of older patients experienced complications [18 of 20 patients] vs 52% of younger patients [8 of 14 patients]; OR for older 6.75 [95% CI 1.1–41.00], p = 0.026), despite there being no significant differences in injury severity score, mean ASIA improvement, steroid administration, or length of stay, as shown in Table 6. Together these results suggest that dopamine is associated with a higher risk of complications than phenylephrine in older patients.

TABLE 3. Vasopressor utilization (n = 34)

Administration Pattern	No. of Patients (%)
Dopamine administered	31 (91.18)
Phenylephrine administered	22 (64.71)
Dopamine administered first	27 (79.42)
Phenylephrine administered first	7 (20.59)
Patients had 2 vasopressors	18 (52.94)
Patients had 2 or more concurrently	12 (35.29)

Complications

Twenty-nine patients experienced at least 1 complication. Table 7 summarizes the complication rates. The most

TABLE 4. Specific complication rates by individual vasopressor

Complication	No. of Patients (%)*	
	Dopamine	Phenylephrine
Patients w/ complications	21 (67.74)	10 (45.45)
Patients w/ multiple complications	2 (6.45)	1 (4.54)
Atrial fibrillation	5 (16.13)	0 (0)
Tachycardia (HR >130 bpm)	9 (29.03)	3 (13.64)
Bradycardia (HR <50 bpm)	4 (12.90)	7 (31.82)
Ventricular tachycardia	3 (9.68)	0 (0)
Troponin levels	2 (6.45)	1 (4.54)

HR = heart rate.
* Percentages are based on the number of patients per category.

common complications were cardiogenic complications associated with vasopressor administration that occurred in 26 patients (76%). Four patients (12%) experienced respiratory failure during the acute phase of their injury. An additional 10 (29%) patients experienced respiratory failure as a complication during the course of their hospitalization. Eight patients (24%) developed urinary tract infections, and 6 patients (18%) developed pneumonia. Five patients (15%) also presented with a concurrent traumatic brain injury. Additional complications and comorbidities included 1 pulmonary embolism without deep vein thrombosis, 1 pneumothorax from central line placement, 1 venous catheter infection, and 1 forehead hematoma and evacuation. No surgical site infections, deep vein thromboses, or strokes were noted.

Discussion

The reviewed cohort of ATCCS patients had cardiogenic complication rates comparable to other studies of vasopressor use in patients with SCI, although our patients received MAP goal support for less than the Level III recommendation of 7 days.[12,17] Given the retrospective nature of this study, it is difficult to determine if the inability to meet MAP goals was triggered by early termination due to complications or provider discretion. Of note, the mean duration of MAP goals was determined to be approximately 4.2 days, as compared with 7 days proposed for SCI patients by Vale et al.[21] While limited by the retrospective nature of this study, we believe that this shorter duration is reflective of the treating surgeon's desire to reduce the morbidity of vasopressor use, particularly after surgical decompression.

Similar to the findings in other recent studies that evaluate vasopressor-related complications for trauma and shock, dopamine was the most common first-line vasopressor administered and associated with a higher risk of complication when compared with phenylephrine.[6,7] Although phenylephrine was associated with lower complication rates, it is not recommended for use in cervical injury due to its risk of inducing bradycardia.[4] Despite these recommendations, we noted that almost half of the patients received treatment with phenylephrine, most commonly as a second-line treatment following complications with dopamine. Given the propensity for cardiovascular complications following SCI, including hypotensive neurogenic shock and autonomic dysreflexia-induced hypertension, optimizing vasopressor support is a critically important issue.[20,27] Considering the high prevalence of ATCCS in elderly patients and our findings of increased risk of dopamine-related complications in elderly patients with ATCCS, further research is needed to determine the optimal MAP guidelines for ATCCS.[14] Since ATCCS is generally a less severe injury than other forms of acute traumatic SCI, caution is warranted when determining supportive interventions, and further research is needed to elucidate the best interventions for this patient population. Our data suggest that any physician administering dopamine in the context of ATCCS, especially for patients older than 55 years, must consider the high complication rates associated with dopamine.

An understanding of vasopressor management protocols for patients with ATCCS will gain even more importance if early data on optimized spinal cord perfusion leads to improved outcomes. Werndle et al. recently reported on a prospective trial, in which intraspinal pressure (ISP) monitors were placed in patients with traumatic SCI.[22] These monitors were used to observe the spinal cord perfusion pressure (SCPP) in 18 patients without any complications such as wound infections or cerebrospinal fluid leaks. Their data directly show that elevated MAP due to vasopressor augmentation does result in a direct increase in ISP and SCPP. Studies in animal models of SCI show that microvascular damage and hypoperfusion is associated with increased degeneration after SCI.[8,11,23] Advanced studies with accurate monitoring via surgically implanted ISP monitors in concordance with neurological improvement scores could contribute to a better understanding of optimal MAP goals in ATCCS patients and provide clear protocols on the issue.

Other Interventions

Our patient population was treated with decompressive surgical intervention at a higher rate and with increased urgency when compared with the published rates in ATCCS and SCI.[1,19] In our cohort we found that 64% of surgical patients (15 of 26 patients) underwent decompression within 24 hours. Conversely, a study examining patients from a similar time period by Aarabi et al. indicated

TABLE 5. Dopamine- vs phenylephrine-induced complications by age*

Cohort	Dopamine Complications	Phenylephrine Complications	OR (95% CI)	p Value
Entire cohort	21/31 (67.74)	10/22 (45.45)	2.520 (0.816–7.782)	0.105
Age >55 yrs	15/18 (83.33)	7/14 (50)	5.000 (0.987–25.341)	**0.044**
Age <55 yrs	6/13 (46.15)	3/8 (37.5)	0.700 (0.116–4.232)	0.697

* Value in boldface is statistically significant.

TABLE 6. Comparison of vasopressor complications by age (age > 55 vs < 55 years)*

Variable	Age >55 (n = 20)	Age <55 (n = 14)	OR (95% CI) (when applicable)	p Value
Mean age (yrs)	72.55 ± 10.875	45.79 ± 7.7073		**<0.01**
Mean ISS	23.73 ± 18.642	23.21 ± 17.564		0.936
Mean MAP goals (hrs)	104.83 ± 52.922	95.57 ± 40.929		0.593
Mean ASIA grade improvement	0.65 ± 0.671	0.93 ± 0.997		0.336
Steroids administered	13 (65.0)	7 (50.0)	1.857 (0.461–7.482)	0.382
ICU LOS (days)	11.70 ± 11.965	11.64 ± 16.402		0.991
Hospital LOS (days)	16.80 ± 15.946	21.29 ± 23.262		0.538
Dopamine administered	18 (90.0)	13 (92.9)	0.692 (0.057–8.470)	0.773
Dopamine complication	15 (83.3)	6 (46.15)	5.833 (1.119–30.403)	**0.029**
Phenylephrine administered	14 (70.0)	8 (57.1)	1.750 (0.420–7.288)	0.44
Phenylephrine complication	7 (50.0)	3 (37.5)	1.667 (0.283–9.822)	0.571
Any vasopressor complication	18 (90.0)	8 (57.1)	6.750 (1.111–41.001)	**0.026**

* Continuous variables are reported as the mean ± SD; categorical variables are reported as number (%). Values in boldface are statistically significant.

that 21% (9 of 42) of their patients with ATCCS underwent rapid surgical decompression within 24 hours.[1] This was consistent with another retrospective study where 24% of ATCCS patients (16 of 67) who underwent decompressive surgery were treated within 24 hours.[19] Ultimately, the decision to perform surgery and the timing of surgery were dependent on the treating surgeon. Given the recent results of the Surgical Timing for Traumatic Cervical Spinal Cord Injury Study (STASCIS), which indicated the benefits of early decompression, we found this difference to be significant and noteworthy.[9] Steroids did not appear to have an impact on the study as the complication rates did not vary between the steroid and nonsteroid groups. The sample size of this study and the lack of significant differences in outcomes and complications between the patients who received steroids and those who did not make it difficult to draw any meaningful conclusions regarding steroids in this population.

Limitations

The primary limitations of this study were the retrospective nature and small sample size of our population. In addition, this retrospective analysis was limited to the course of acute recovery, and neurological outcomes in long-term follow-up may have provided additional insight into the effect of vasopressors. The small sample size is reflective of the limited number of central cord injuries seen at an individual institution. This limitation may have prevented several associations from reaching significance with $p \leq 0.05$, as many associations approached this statistical cutoff. At our institution, we have adhered to protocol-based management as strictly as possible for several years. As such, nearly all of our patients with acute SCI, including ATCCS, were managed with vasopressors and MAP goals. Though we believe that this practice improves the quality of the care that we provide to patients, the downside is that this has resulted in the lack of a control group for this study. Finally, quantification of ATCCS severity was performed utilizing the ASIA grading system, and this has limitations given the asymmetrical involvement of the upper extremities associated with ATCCS.

TABLE 7. Complication rate (n = 34)

Complication	No. of Patients (%)
Pneumonia	6 (17.65)
Respiratory failure on arrival	4 (11.76)
Respiratory failure in hospital	10 (29.41)
Urinary tract infection	8 (23.53)
Tracheostomy	3 (8.82)
Gastrostomy	2 (5.88)
Cardiogenic	26 (76.47)
Complication of any kind	29 (85.29)

Conclusions

Our results provide compelling data concerning vasopressor-associated complication rates in patients with central cord syndrome. We observed a complication rate of 85% for ATCCS injuries, with 76% of patients experiencing cardiogenic complications associated with vasopressor administration. As the US population continues to age, we anticipate a rise in this condition given its increased incidence in the elderly. Based on the results of our analysis, careful consideration of the risks should be made before administering dopamine in the context of ATCCS in patients over 55 years.

Establishing clear MAP guidelines for ATCCS, in addition to SCI in general, is extremely important and warrants thorough investigation. Ideally, we encourage a multicenter prospective study to elucidate the risk-benefit ratio for SCI with a subanalysis of central cord patients. Given the difficulty of establishing this type of protocol, a more rapid and financially obtainable solution may be to conduct a large, multicenter, retrospective review of SCI patients receiving vasopressors in order to compare cross-institutional outcomes and complications while also providing the statistical power to make more confident as-

sessments of MAP goals. A subgroup analysis of central cord injuries in this type of study would also be extremely valuable for elucidating additional knowledge regarding ATCCS.

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Author Contributions

Conception and design: all authors. Acquisition of data: Readdy, Whetstone, Inoue. Analysis and interpretation of data: Dhall, Readdy, Whetstone. Drafting the article: Dhall, Readdy, Talbott. Critically revising the article: Dhall, Readdy, Whetstone, Ferguson, Talbott, Saigal, Bresnahan, Pan, Manley. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dhall. Statistical analysis: Readdy, Ferguson, Beattie. Study supervision: Dhall, Manley.

Supplemental Information

Previous Presentation

Portions of this work were accepted and presented as an oral presentation by Dr. Sanjay Dhall to the Annual Meeting of the Congress of Neurological Surgeons, Boston, Massachusetts, October 18–22, 2014.

Correspondence

Sanjay Dhall, Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Ave., Box 0112, San Francisco, CA 94143. email: sanjaydhall@gmail.com.

Failure of Mean Arterial Pressure Goals to Improve Outcomes Following Penetrating Spinal Cord Injury

William J. Readdy, BS*‡
Rajiv Saigal, MD, PhD*‡
William D. Whetstone, MD‡§
Anthony N. Mefford, BS‡
Adam R. Ferguson, PhD‡
Jason F. Talbott, MD, PhD‡¶
Tomoo Inoue, MD, PhD‡
Jacqueline C. Bresnahan, PhD‡
Michael S. Beattie, PhD‡
Jonathan Pan, MD, PhD‡||
Geoffrey T. Manley, MD, PhD‡
Sanjay S. Dhall, MD‡

‡Brain and Spinal Injury Center, Departments of Neurological Surgery, §Emergency Medicine, ¶Radiology and Biomedical Imaging, and ||Anesthesia, University of California, San Francisco, San Francisco, California

*These authors contributed equally to this work.

Correspondence:
Sanjay S. Dhall, MD,
Department of Neurological Surgery,
University of California,
San Francisco,
505 Parnassus Ave, Box 0112,
San Francisco,
CA 94143.
E-mail: sanjaydhall@gmail.com

Received, September 2, 2015.
Accepted, February 8, 2016.
Published Online, May 3, 2016.

BACKGROUND: Increased spinal cord perfusion and blood pressure goals have been recommended for spinal cord injury (SCI). Penetrating SCI is associated with poor prognosis, but there is a paucity of literature examining the role of vasopressor administration for the maintenance of mean arterial pressure (MAP) goals in this patient population.

OBJECTIVE: To elucidate this topic and to determine the efficacy of vasopressor administration in penetrating SCI by examining a case series of consecutive penetrating SCIs.

METHODS: We reviewed consecutive patients with complete penetrating SCI who met inclusion and exclusion criteria, including the administration of vasopressors to maintain MAP goals. We identified 14 patients with complete penetrating SCIs with an admission American Spinal Injury Association grade of A from 2005 to 2011. The neurological recovery, complications, interventions, and vasopressor administration strategies were reviewed and compared with those of a cohort with complete blunt SCI.

RESULTS: In our patient population, only 1 patient with penetrating SCI (7.1%) experienced neurological recovery, as determined by improvement in the American Spinal Injury Association grade, despite the administration of vasopressors for supraphysiological MAP goals for an average of 101.07 ± 34.96 hours. Furthermore, 71.43% of patients with penetrating SCI treated with vasopressors experienced associated cardiogenic complications.

CONCLUSION: Given the decreased likelihood of neurological improvement in penetrating injuries, it may be important to re-examine intervention strategies in this population. Specifically, the use of vasopressors, in particular dopamine, with their associated complications is more likely to cause complications than to result in neurological improvement. Our experience shows that patients with acute penetrating SCI are unlikely to recover, despite aggressive cardiopulmonary management.

KEY WORDS: Dopamine, Gunshot wound, Penetrating injury, Spinal cord perfusion, Traumatic spinal cord injury, Vasopressors

Neurosurgery 79:708–714, 2016 DOI: 10.1227/NEU.0000000000001249 www.neurosurgery-online.com

Spinal cord injury (SCI) is an incredibly serious and grievous injury that can have drastic costs, both financially and emotionally.[1,2] Recent statistics estimate the incidence of spinal cord injuries in the United States to be 12 000 annually.[1] The financial implication of these injuries, in particular complete injuries, can be significant, ranging from more than $1.4 million to $4.5 million, depending on age and level of injury.[1] Given the rising incidence and the extreme emotional and fiscal costs, recent studies have looked at the epidemiology of SCI. Chen et al[3] noted that gunshot wounds (GSWs), the most common type of penetrating SCI, are associated with the highest rates of neurological impairment on admission. Given the high rate of impairment, the rise in civilian GSWs, and the impact of penetrating injury on our military, there has been significant research in the field of penetrating SCI in recent years.[4-6]

ABBREVIATIONS: ASIA, American Spinal Injury Association; **MAP,** mean arterial pressure; **SCI,** spinal cord injury

A recent literature review by Sidhu et al[7] was notable for documenting a scarcity of data in the literature to guide surgical timing and prognosis for penetrating SCIs. Their review produced low-level recommendations and failed to convincingly address many critical management questions with regard to these unique injuries. Additionally, the majority of research on the topic has been published on cervical injury, with the results being extrapolated to thoracolumbar management.[6,8]

To the best of our knowledge, no reports on the specific management of mean arterial pressure (MAP) goals in penetrating SCI currently exist in the literature. One recent comprehensive study on cervical penetrating injury by Beaty et al[6] provided important information on neurological improvement and surgical interventions in cervical GSWs. In their study, the authors indicate that all patients received vasopressors to maintain MAP goals >80 mm Hg, as has been common in SCI since the recommendation of MAP goals by Vale et al[9] in 1997. However, Beaty et al[6] did not elaborate on evidence-based justification for vasopressor administration, stating only that it was the standard of care at their institution.[6] These MAP goals have been supported by the 2013 American Association of Neurological Surgeons guidelines for cervical SCI; however, the 2013 author group noted that limited evidence exists on the topic and recommended prospective studies to provide a better understanding of MAP guidelines.[10] Extrapolating these guidelines universally to all SCIs, particularly given the unique clinical characteristics of penetrating SCI, raises additional concerns.

In this study, we attempted to elucidate the neurological recovery in the context of vasopressor administration for complete penetrating injuries. Given the poor prognosis for complete SCIs, and penetrating injuries in particular, we anticipated that these patients would be less likely to benefit from vasopressor administration than patients with other forms of SCI.[3,11,12]

METHODS

Study Design

This retrospective study was conducted with approval of the University of San Francisco's Committee on Human Research. The study received an exemption from informed consent because of its classification as minimal risk. During the study, all data were collected and stored in REDCap (Research Electronic Data Capture), a Cloud-based platform hosted by the University of California, to ensure data integrity and security.

Participants

An initial patient population was derived from a database maintained by the Department of Neurosurgery and Brain and Spinal Cord Injury Center at the San Francisco General Hospital, a level I trauma center. At our institution, the standard of care involves the maintenance of MAP levels >85 mm Hg for all patients suffering an acute SCI, blunt or penetrating, for approximately 7 days. This database contains 131 sequential patients who met the following inclusion criteria: presented with an acute traumatic SCI between 2005 and 2011, received vasopressor support and blood pressure resuscitation for a minimum of 24 hours requiring care in the intensive care unit, and were >18 years of age at the time of injury. From this group, we identified patients who further met the following inclusion criteria: presence of a complete injury as indicated by American Spinal Injury Association (ASIA) grade A on admission and presence of a penetrating injury, including GSWs and stab wounds. ASIA grade was used as an indicator for neurological function, given its consistent validation and current evidence-based recommendations.[13,14] After the patient population was determined, preselected variables were analyzed. A second cohort with complete blunt injuries was identified for comparison. This cohort was determined from sequential patients with blunt trauma during the same time period who met the same inclusion criteria as the penetrating injury group. Although the pathophysiology of penetrating SCI (particularly GSW) is quite different from that of blunt SCI, we included patients with blunt injury in this study to highlight the dramatic difference in potential recovery between the 2 groups. We hypothesize that there will be significant and striking differences in the rates of recovery for patients with blunt injury compared with patients with penetrating injury despite vasopressor administration in both cohorts.

Variables

Demographic variables, including age, date of injury, characteristics, and level of injury, and admission ASIA score were identified from the Department of Neurosurgery database. At the conclusion of the patient identification, a blinded researcher performed a retrospective chart review of all patients who satisfied inclusion and exclusion criteria. This reviewer examined emergency medical services transport logs, emergency room documentation, progress notes, pharmacy records, operative notes, rehabilitation notes, consent forms, and discharge summaries to collect relevant data. The researcher also independently verified all information from the departmental database. By the conclusion of the chart review process, 2 authors (W.D.W. and W.J.R.) had each examined all of the records.

During the chart review, variables associated with the injury were identified. They included injury severity scores, details of the mechanism of injury, and information on the emergency triaging of these patients. Additionally, courses of treatment, including procedures, interventions, and pharmacological treatment, were identified. Specifically, surgical timing, the use of advanced medical care, including invasive lines, gastrostomies, and tracheostomies, and the patterns of vasopressor administration were reviewed. In reviewing the pattern of vasopressor administration, the researchers identified the course of MAP goal parameters, the vasopressors used, and the complications associated with those vasopressors. Vasopressor-linked cardiogenic complications were defined as significant tachycardia (heart rate > 130 bpm), significant bradycardia (heart rate < 50 bpm), ventricular tachycardia, atrial fibrillation, and elevated troponin levels. The primary outcomes of interest were neurological improvement, as indicated by a comparison of ASIA grades from admission to discharge, and vasopressor-associated complications. Secondary outcomes included length of stay in both the intensive care unit and the hospital and hospital complications such as urinary tract infections, pneumonias, respiratory failure, and pulmonary embolisms.

Statistical Methods

After data collection, the patient population with penetrating injury was compared with the population with blunt injury. All statistical analyses were conducted with standardized statistical software (IBM SPSS Statistics for Macintosh, version 22.0, IBM Corp, Armonk, New York; released 2013). Categorical data were assessed for incidence rates and reported as n/N (percent incidence). Continuous variables were assessed and expressed as mean ± SD. Univariate analysis was conducted via cross-tabulations with

the Pearson χ^2 test for all categorical comparisons. The *t*-tests were used for univariate comparisons of continuous variables. Multivariate analysis of categorical variables was conducted with additional cross-tabulations and χ^2 testing. For all variable testing, statistical significance was set at $P < .05$. These methods were used to compare the outcome measures between cohorts while observing the descriptive variables for any confounding.

RESULTS

Participants

From the original database of 131 patients, we identified 63 patients who met our criteria for blunt or penetrating mechanisms of injury. Of those patients, 36 had complete injuries, as indicated by an admission ASIA grade of A. Of the 36 patients, 14 had penetrating injuries and the remaining 22 patients had blunt injuries.

Descriptive and Primary Outcome Data

The characteristics of patients with penetrating SCIs are shown in Table 1. The mean age of the patients with penetrating injury was 28.43 ± 9 years. The mean injury severity score was 32.36 ± 15.47, and the average duration of vasopressor administration for MAP goals was 101.07 ± 34.96 hours. Eleven patients (78.5%) suffered thoracic injuries, and 9 patients (64.29%) suffered hemorrhagic SCI. Notably, only 1 patient experienced any form of neurological recovery, improving from ASIA grade A on admission to ASIA grade B at discharge. The remaining 13 patients showed no neurological improvement. In contrast, the rate of improvement was significantly higher in the patient population with blunt injury, with 36.36% of the patients with complete blunt injury experiencing at least some degree of neurological recovery. Mortality was observed in 1 patient with penetrating injury who presented with a complete transection of the right vertebral artery leading to eventual brain death, at which time the family withdrew care.

Main Results

Interventions and Vasopressor Administration

Cardiogenic complications occurred in 10 of 14 patients (71.43%) with penetrating injury receiving vasopressors for supratherapeutic MAP goals, as shown in Table 2. This was not statistically different from the vasopressor-induced complication rate in patients with complete blunt SCI at this institution (odds ratio, 1.80; 95% confidence interval, 0.37-8.80; $P = .47$). In all patients, dopamine was associated with higher rates of complications than phenylephrine. MAP goals were maintained for approximately the same amount of time in each group, with

TABLE 1. Comparison of Penetrating and Blunt Complete Injuries[a]

Variable[b]	Penetrating (n = 14)	Blunt (n = 22)	Odds Ratio (95% Confidence Interval) When Applicable	*P*
Sex, n (%)			2.250 (0.385-13.166)	.36
Male	12 (85.71)	16 (72.72)		
Female	2 (14.29)	6 (27.27)		
Age, yr[c]	28.43 ± 9.00	46.36 ± 20.73		.001
Injury severity score	32.36 ± 15.47	36.95 ± 14.64		.38
MAP goal duration, h	101.07 ± 34.96	124.18 ± 45.91		.10
MAP goals missed, total h	36.86 ± 31.31	27.95 ± 23.45		.37
Steroids administered, n (%)	0 (0)	16 (72.72)		
Intensive care unit length of stay, d	14.00 ± 16.03	27.09 ± 25.73		.10
Hospital length of stay, d	31.64 ± 34.26	40.64 ± 36.64		.47
Mortality rate, n (%)	1 (7.14)	2 (9.09)		.84
Neurological improvement, n (%)[d]			7.43 (0.81-67.83)	.048
Improved	1 (7.14)	8 (36.36)		
No improvement[d]	13 (92.85)	14 (63.64)		
Level of injury, n (%)[d]				.04
Cervical	2 (14.29)	12 (54.55)		
Thoracic	11 (78.75)	8 (36.36)		
Lumbar/sacral	1 (7.14)	2 (9.09)		
Hemorrhagic injury, n (%)[d]	9 (64.29)	2 (9.09)	18.00 (2.92-110.96)	<.001
Surgical management, n (%)[d]				.03
Nonoperative	8 (57.14)	5 (22.73)		
Surgery ≤24 h	2 (14.29)	13 (59.09)		
Surgery >24 h	4 (28.57)	4 (18.18)		

[a]MAP, mean arterial pressure.
[b]Continuous variables are reported as mean ± SD; categorical data are reported as n (incidence percent).
[c]*P* is significant by *t*-test.
[d]*P* is significant by χ^2.

TABLE 2. Complications and Comorbidities for Complete Penetrating and Blunt Injuries

Variables	Penetrating (n = 14), n (%)	Blunt (n = 22), n (%)	Odds Ratio (95% Confidence Interval) When Applicable	*P*
Pneumonia	4 (28.57)	11 (50)	2.50 (0.59-10.44)	.20
Respiratory failure	10 (71.43)	19 (86.36)	2.53 (0.47-13.61)	.27
Urinary tract infection	4 (28.57)	10 (45.45)	2.08 (0.50-8.72)	.31
Tracheostomy	3 (21.43)	9 (40.90)	2.54 (0.55-11.76)	.23
Gastrostomy	1 (7.14)	3 (13.64)	2.053 (0.19-21.97)	.54
Deep vein thrombosis	2 (14.29)	2 (9.09)	1.667 (0.21-13.43)	.63
Pulmonary embolism	1 (7.14)	0 (0)		
Cardiogenic	10 (71.43)	18 (81.82)	1.80 (0.37-8.80)	.47
Complication of any kind	13 (92.86)	21 (95.45)	1.62 (0.9-28.12)	.74
Concurrent traumatic brain injury	0 (0)	8 (36.36)		
Extremity fracture	1 (7.14)	4 (18.18)	2.89 (0.29-28.94)	.35
Vertebral artery injury	2 (14.29)	3 (13.64)	1.06 (0.153-7.270)	.96

patients with penetrating SCI receiving 101.1 hours of goals and blunt SCI patients receiving 124.2 hours. There was no statistical difference between the 2 groups ($P = .10$). Additionally, 2 patients who transferred early in their hospital course affected the length of stay in the group with penetrating injury. These patients were transferred to another facility's acute intensive care unit during the early portion of their hospitalization for financial reasons.

Neurological Outcomes

A significant difference in neurological improvement was observed between the 2 groups, as shown in the Figure. Complete blunt injuries were more likely to improve compared with complete penetrating injuries (blunt, 36.36% [8 of 22 patients] vs penetrating, 7.14% [1 of 14]; odds ratio for blunt injuries, 7.429; 95% confidence interval, 0.814-67.831; $P = .048$). These results quantify the poor prognosis of complete penetrating injuries compared with blunt SCI.

Complications

Table 2 shows that there were no statistical differences in complication rates between patients with penetrating injury and patients with blunt injury. No patients experienced alcohol withdrawal or documented strokes during the course of their hospitalization. Cardiopulmonary complications were the most common type of complication. Additional common complications included nosocomial infections such as ventilator-associated pneumonia and urinary tract infections. The overall complication rate for all patients in both groups was 94.44% (34 of 36 patients). Two patients in each cohort developed deep vein thrombosis, and 1 patient had progression resulting in a pulmonary embolism. All patients with deep vein thrombosis were treated with anticoagulation and antiplatelet medications. As shown in Table 3, there were no differences in the pharmacologic management of the two groups. However, as indicated by Table 4, the rate of vasopressor-induced complications was higher than phenylephrine in the entire cohort and the blunt subgroup.

DISCUSSION

Key Results

Although many studies have indicated that complete penetrating injuries have a poor prognosis, there is a paucity of direct comparison with other mechanisms of complete injury.[6,15,16] One recent study notes that penetrating injuries "are more likely to result in complete neurological deficits than blunt trauma. However in reviewing prior case series, outcome data are rarely presented in a discrete and quantifiable manner."[6] Our results provide quantitative support for the long-standing assertion that complete penetrating injuries are less likely to improve compared with blunt injuries, even in the setting of vasopressor resuscitation. This significant decrease in improvement warrants further investigation. In particular, the administration of vasopressors and their associated complications should be evaluated.

Limitations and Generalizability

Our study design provides limitations that may affect the generalizability of our findings. In particular, the retrospective nature limits the understanding of the patient's entire clinical course. However, because no prospective studies have examined the role of MAP resuscitation in this population, we believe our findings to be an important addition to the literature. Additionally, given this institution's role as a public trauma hospital, follow-up is limited to neurological assessment at the time of discharge. The study was also limited by a small sample size. Given the severe and rare nature of complete penetrating injuries, the number of cases identified will be limited in a review of a single institution. It is notable that patients in the penetrating group were less likely to receive rapid surgical intervention and had a higher preponderance of thoracic injuries, which could serve as possible confounders. Adherence to the current American Association of Neurological Surgeons/Congress of Neurological Surgeons guidelines on the maintenance of MAP goals also precluded the establishment of a control group of patients with penetrating SCI who did not

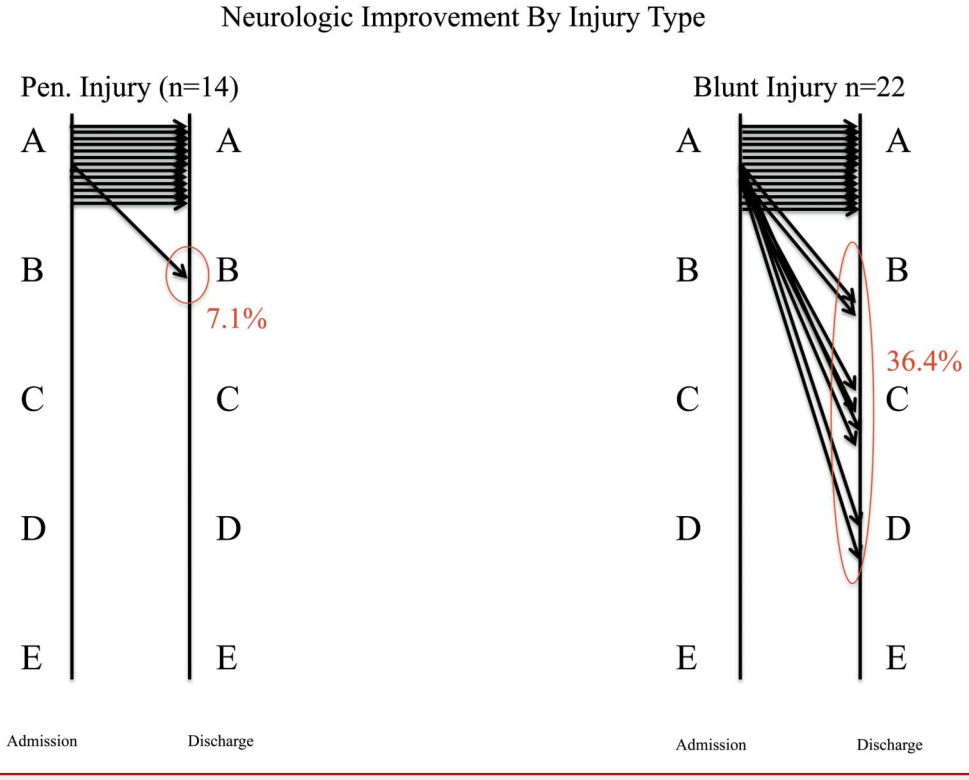

FIGURE. *Initial and discharge American Spinal Injury Association (ASIA) grades for all patients in our cohort plotted within each mechanism of injury subgroup. The percentage of patients within each subgroup who showed neurological improvement as determined by ASIA grade is circled and listed to the right of the discharge ASIA grades. Color version available online only.*

receive vasopressors because achieving MAP goals with vasopressor therapy is the standard of care at our institution. In the future, a standardized, multicenter review with statistical analysis controlling for cofounding variables may provide additional and important knowledge in the field.

Interpretation

Vasopressor administration for MAP goals has become the standard of care for SCI at many institutions, based primarily on the work of 2 retrospective studies from the 1990s.[9,17] It has been postulated that MAP augmentation may increase perfusion to the spinal cord and prevent lasting injury.[18] SCI has been associated with autonomic dysreflexia and possible episodes of hypotension. It has been proposed that elevated MAP goals increase spinal cord perfusion, reducing hypotensive episodes and maintaining cellular nutrient levels. In complete penetrating injury, there is complete transection of the spinal cord. Complete transections can be anatomic, in the case of projectile-based and stabbing injuries, or functional, in the case of blast-based penetrating injury. In this setting, the delivery of additional nutrients and the avoidance of hypotensive episodes may not provide any benefit

TABLE 3. Comparison of Complete Penetrating and Blunt Injuries

Variables	Penetrating (n = 14), n (%)	Blunt (n = 22), n (%)	Odds Ratio (95% Confidence Interval) When Applicable	*P*
Distribution of treatments				
Dopamine given	11 (78.57)	18 (81.81)	1.23 (0.23-6.55)	.81
Phenylephrine given	10 (71.43)	20 (90.90)	4.00 (0.62-25.68)	.13
Total cardiogenic complications	10 (71.43)	18 (81.82)	1.80 (0.37-8.80)	.47
Dopamine-associated complications	7 (50.0)	15 (68.18)	2.14 (0.54-8.51)	.28
Phenylephrine-associated complications	5 (35.71)	7 (31.81)	1.19 (0.29-4.90)	.81

TABLE 4. Comparison of Dopamine and Phenylephrine Complications by Mechanism of Injury

Cohort	Dopamine Complications, n/N (%)	Phenylephrine Complications, n/N (%)	Odds Ratio (95% Confidence Interval) When Applicable	*P*
Entire cohort[a]	22/29 (75.86)	12/30 (40.0)	4.7 (1.54-14.47)	.005
Penetrating injury	7/11 (63.63)	5/10 (50.0)	1.75 (0.31-10.02)	.53
Blunt injury[a]	15/18 (83.33)	7/20 (35.0)	9.29 (1.98-43.45)	.003

[a]*P* is significant by χ^2.

with regard to progressive cell death and avoidance of permanent injury because the spinal cord has been completely severed.

However, Plurad et al[19] recently showed that the administration of vasopressors was independently associated with mortality in trauma patients, excluding those with traumatic brain injury and SCI. In an effort to translate this information to SCI patients, Inoue et al[20] recently published a series showing the high complication rates of vasopressor administration in SCI. High vasopressor-associated complication rates were also seen in a recent study of patients with acute traumatic central cord syndrome. The results called into question the clinical benefit of applying MAP goals in the population with acute traumatic central cord syndrome.[21] Our series similarly demonstrates high complication rates within the subset of patients with penetrating SCIs. Penetrating injuries are also associated with a poor prognosis because they often result in complete cord transection and, as shown by our series of cases, in hemorrhagic injury. Hemorrhagic SCI is associated with poor prognosis, and the increased prevalence in penetrating injuries is not surprising, given their decreased neurological improvement.[22,23]

Of particular concern is the significant rate of complications associated with dopamine use as the most common first-line vasopressor. Dopamine produced significantly more complications in the blunt injury group and the cohort as a whole than other vasopressors. These results support the recent literature on SCI and traumatic injury as a whole.[20,24,25] In a randomized controlled trial, De Backer et al[24] showed that dopamine was linked to significantly more complications and adverse events compared with norepinephrine for vasopressor administration. This significant finding was supported by a meta-analysis in 2012 and the results of a recent study of SCI patients.[20,25]

Given the high rate of dopamine-associated complications and the nearly universal poor prognosis of complete penetrating SCIs, the seemingly small potential benefit of administration of vasopressors in these patients may be exceeded by the risk of complications. Additionally, we believe that a multicenter, prospective, observational study is needed to provide a better understanding of the benefits of vasopressor administration in the context of this patient population and to produce clear and specific guidelines for best practice.

The need for a prospective study is enhanced by the rising rates of penetrating SCIs in both civilian and military populations.[4,26-28] Recent studies showed that penetrating SCI was a significant issue for military personnel serving in Iraq and Afghanistan, possibly as a result of the increase in improvised explosive devices, which are associated with shrapnel-based transection, and blast injury patterns. Additionally, the authors found a trend toward decreased neurological recovery in these patients.[26] The impact of this injury pattern on military populations and civilians further indicates the need for prospective research on this topic.

CONCLUSION

Given the low incidence of neurological recovery in complete penetrating injuries, the benefit of vasopressor administration, particularly dopamine, should be weighed against the high complication rates. Our results indicate that patients with complete penetrating injury experience high rates of complications secondary to blood pressure augmentation for the maintenance of MAP goals with minimal neurological benefit.

Disclosures

Partial support for this study was provided by a Department of Defense Congressionally Directed Medical Research Programs award (SC120259) to Drs Beattie, Manley, Bresnahan, Whetstone, and Ferguson. Dr Dhall has received speaker honoraria from DePuy and Globus. Dr Talbott is a Data Monitoring Committee member for StemCells Inc. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The current era in medicine will be defined by how well individual institutions and physicians measure in terms of quality of healthcare delivery and patient safety. The Institute of Health Improvement has identified reducing variation as an important change concept for quality improvement. By reducing variation in healthcare delivery, one can expect to improve the predictability of outcomes and to decrease the frequency of poor results.[1] Protocols are universally accepted as an effective method by various high-reliability industries (eg, airlines, amusement parks) for reducing variation and thereby optimizing efficiency and avoiding complications. In medicine, disease-specific protocols are used by high-reliability organizations to improve patient outcomes. Ideally, protocols arise from evidence-based guidelines and are subject to the plan-do-study-act (PDSA) cycle for iterative assessment of change.

This important study by Readdy et al is an excellent example of using a disease-specific protocol to improve quality and patient safety. The authors report the implementation of a standardized mean arterial pressure (MAP) goal protocol for the management of patients with spinal cord injury (SCI). The basis for this protocol is from evidence-based guidelines published and recently updated in this journal.[2] The authors present 2 distinct groups with American Spinal Injury Association (ASIA) grade A SCI who underwent this MAP goal protocol: those with blunt SCI and those with penetrating SCI. The blunt SCI group demonstrated a remarkably high rate of neurological recovery, with 27% improving from an ASIA grade A to either an ASIA grade C or D during a relatively short follow-up period. No patient in the penetrating SCI group showed any motor recovery, with only 1 patient (7%) improving to an ASIA grade B and 93% remaining ASIA grade A. Both groups demonstrated similar occurrence of cardiogenic complications that may have been related to protocol-based vasopressor administration.

Contrasting the blunt and penetrating SCI outcomes in this study is an apples-to-oranges comparison. There were important clinical differences between the groups beyond mechanism of injury, including the higher proportion of cervical injuries and operative patients in the blunt SCI group. Therefore, conclusions about the efficacy of an MAP goal protocol for SCI must be made separately for each group. A true control population for the penetrating SCI group would be patients who did not undergo the MAP goal protocol. One can hypothesize, however, as to why the penetrating injuries did not demonstrate neurological recovery. Increasing spinal cord perfusion pressure presumably improves function by salvaging at-risk tissue from further secondary injury. After penetrating trauma, the spinal cord likely suffers most of its functional loss at the time of primary injury and therefore has limited potential for rescue.

The authors are to be commended for making an important contribution to SCI healthcare quality and patient safety by implementing an evidence-based protocol, studying the effect, and reporting the results. The next phase of the PDSA cycle for quality improvement is to expand this change to a larger scale to determine whether the change should be adopted more widely. There is still a question of whether this MAP goal protocol should be continued for specifically penetrating injuries. Following the PDSA process, further iterative changes should be made until a positive result is identified or until it is clear that the protocol should be discontinued for this specific population. As further data become available, I expect more institutions will follow the example set by these authors and implement SCI management protocols. This will lead to reduced variation in care for an otherwise complex, challenging condition. The goals will be to optimize reliability of patient outcomes and ultimately to improve quality of care.

Daniel J. Hoh
Gainesville, Florida

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JNS SPINE

CLINICAL ARTICLE

The Brain and Spinal Injury Center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings

Jason F. Talbott, MD, PhD,[1,4] William D. Whetstone, MD,[2] William J. Readdy, BS,[3] Adam R. Ferguson, PhD,[3,4] Jacqueline C. Bresnahan, PhD,[3,4] Rajiv Saigal, MD, PhD,[3,4] Gregory W. J. Hawryluk, MD, PhD,[3,4] Michael S. Beattie, PhD,[3,4] Marc C. Mabray, MD,[1] Jonathan Z. Pan, MD, PhD,[4,5] Geoffrey T. Manley, MD, PhD,[3,4] and Sanjay S. Dhall, MD[3,4]

Departments of [1]Radiology and Biomedical Imaging, [3]Neurological Surgery, and [5]Anesthesia and Perioperative Care, University of California; and [2]Department of Emergency Medicine and [4]Brain and Spinal Injury Center, San Francisco General Hospital, San Francisco, California

OBJECT Previous studies that have evaluated the prognostic value of abnormal changes in signals on T2-weighted MRI scans of an injured spinal cord have focused on the longitudinal extent of this signal abnormality in the sagittal plane. Although the transverse extent of injury and the degree of spared spinal cord white matter have been shown to be important for predicting outcomes in preclinical animal models of spinal cord injury (SCI), surprisingly little is known about the prognostic value of altered T2 relaxivity in humans in the axial plane.

METHODS The authors undertook a retrospective chart review of 60 patients who met the inclusion criteria of this study and presented to the authors' Level I trauma center with an acute blunt traumatic cervical SCI. Within 48 hours of admission, all patients underwent MRI examination, which included axial and sagittal T2 images. Neurological symptoms, evaluated with the grades according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS), at the time of admission and at hospital discharge were correlated with MRI findings. Five distinct patterns of intramedullary spinal cord T2 signal abnormality were defined in the axial plane at the injury epicenter. These patterns were assigned ordinal values ranging from 0 to 4, referred to as the Brain and Spinal Injury Center (BASIC) scores, which encompassed the spectrum of SCI severity.

RESULTS The BASIC score strongly correlated with neurological symptoms at the time of both hospital admission and discharge. It also distinguished patients initially presenting with complete injury who improved by at least one AIS grade by the time of discharge from those whose injury did not improve. The authors' proposed score was rapid to apply and showed excellent interrater reliability.

CONCLUSIONS The authors describe a novel 5-point ordinal MRI score for classifying acute SCIs on the basis of axial T2-weighted imaging. The proposed BASIC score stratifies the SCIs according to the extent of transverse T2 signal abnormality during the acute phase of the injury. The new score improves on current MRI-based prognostic descriptions for SCI by reflecting functionally and anatomically significant patterns of intramedullary T2 signal abnormality in the axial plane.

http://thejns.org/doi/abs/10.3171/2015.1.SPINE141033

KEY WORDS spinal cord injury; MRI; T2; ASIA; contusion; BASIC; trauma

ABBREVIATIONS AIS = American Spinal Injury Association (ASIA) Impairment Scale; BASIC = Brain and Spinal Injury Center; PACS = picture archiving and communication system; SCI = spinal cord injury.

SUBMITTED October 6, 2014. **ACCEPTED** January 21, 2015.

INCLUDE WHEN CITING Published online July 10, 2015; DOI: 10.3171/2015.1.SPINE141033.

DISCLOSURE Partial support for this study was provided by a Department of Defense Congressionally Directed Medical Research Programs award (SC140137) to Drs. Beattie, Manley, Bresnahan, Whetstone, and Ferguson. Dr. Dhall has received speaker honoraria from DePuy and Globus.

Following the advent and widespread implementation of MRI in the 1980s, many researchers have investigated the prognostic value of MRI findings in assessing acute spinal cord injury (SCI). In particular, the prognostic value of abnormalities in T2-weighted MRI signals has been extensively explored.[3,4,10,13,15,19,27,30,32,42] In the acute phase, a T2 signal abnormality within the injured spinal cord has been attributed to various underlying pathological changes in both human and animal studies.[8,25,26,31] For example, a T2 hypointense signal reflects the susceptibility-related T2-shortening effect of intracellular deoxyhemoglobin during the acute and subacute phases of hemorrhage.[14] A T2 hyperintense signal is less specific and probably reflects a combination of vasogenic edema, cytotoxic edema, axonolysis, myelinolysis, inflammatory cellular infiltrate, and petechial hemorrhage.[25,28,31] Early MRI-based classification systems for acute SCIs defined 3 distinct patterns of intramedullary signal change: Type I, with diffuse T2 hypointensity; Type II, with intramedullary T2 hyperintensity; and Type III, with central T2 hypointensity and a surrounding hyperintense signal.[3,10,20] Modification of these descriptions in subsequent studies eliminated the Type I pattern because a T2 hypointense hemorrhage was not routinely observed without a significant surrounding T2 hyperintense edema.[12,33]

A more widely adopted classification system defines 4 distinct injury patterns as assessed on a sagittal T2-weighted MRI sequence.[1,4,23,33,35] Pattern 1 represents a normal spinal cord signal; Pattern 2 shows a T2 hyperintense intramedullary edema, with its longitudinal extent confined to a single vertebral level; Pattern 3 indicates a multilevel edema; and Pattern 4 includes a mixed hemorrhage and edema.[4] Such classification systems have been shown to provide measures that correlate with injury severity and that supplement other clinical measures for predicting clinical outcome.[1,11,12,23,32,35]

Patterns based on sagittal T2-weighted MRI signals are most accurate at predicting outcomes when patients have very mild (that is, Pattern 1, indicating a normal cord signal) or severe (Pattern 4, with hemorrhage and edema) injury.[4] However, in the setting of nonhemorrhagic intramedullary T2 hyperintensity, there is tremendous variability in clinical outcomes. For example, in a meta-analysis, Bozzo et al. reported that among 49 patients presenting with Pattern 3 edema (that is, with multilevel T2 hyperintensity), the injury severity grades of the American Spinal Injury Association (ASIA) Impairment Scale (AIS) were nearly equally distributed at the follow-up: 27% of these patients had an AIS grade of A, 22% of B, 24% of C, and 24% of D.[4] This wide variability in outcome data is in part related to the arbitrary measurement of the longitudinal extent of the T2 signal relative to the height of the vertebral body, in addition to the nonspecific nature of T2 hyperintensity in the spinal cord. Histopathological studies of SCI in animals have revealed that longitudinal measurements do not correlate with functional recovery as well as axial or cross-sectional area does.[5] In addition, translational studies of axial T2 images in rats have indicated a strong correspondence of axial MRI findings with microscopic histopathology and functional recovery.[28]

Given the limitations of previous longitudinal MRI-based measures of intramedullary signal change and the paucity of axial T2 data on SCIs, we sought to develop a simple and reproducible classification system for blunt traumatic SCI that is based on the transverse extent of intramedullary T2-weighted MRI signal abnormality during the acute phase of injury. We hypothesized that such a classification system would reflect the functionally relevant anatomical distribution of pathological MRI signal changes and therefore yield valuable diagnostic and prognostic information. In this study, we aimed to assess the reliability and validity of this MRI-based classification system in a cohort of patients with blunt traumatic SCIs.

Methods

Patient Selection

We performed a retrospective chart review to evaluate the diagnostic and prognostic values of axial T2-weighted MRI findings for rating the severity of acute SCIs in patients admitted to San Francisco General Hospital, a Level I trauma center, between January 2005 and December 2011. This study was approved by the internal review board of the University of California. Patients' records were reviewed in a Department of Neurosurgery database and in cross-referencing trauma logs, with searchable terms and by using electronic medical records (San Francisco, CA). From this database, we retrospectively identified the records of 131 patients who had a principal diagnosis of SCI (codes 953–957 designating discharge diagnoses) according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Of these patients, 92 had cervical levels of injury, 60 of whom met this study's inclusion criteria.

To be eligible for this study, patients had to be 18 years of age or older; had to have an MRI examination performed within 48 hours of admission which, at a minimum, included T2-weighted images of the cervical spine in both the axial and sagittal planes; and had to have a documented AIS grading performed both at the time of admission and at a follow-up (performed at the time of discharge from the acute-care hospital). We excluded patients younger than 18 years; those with an SCI related to penetrating trauma or with imaging evidence of complete spinal cord transection; and those with MRI studies degraded by motion or other artifacts such that T2-weighted images were nondiagnostic as assessed by a neuroradiologist (J.F.T.). Patients who underwent surgical decompression, fusion, or both before the MRI examination were also excluded. SCI-trained physiatrists and neurosurgical and neurocritical care attending physicians performed the AIS grading. All eligible patients' AIS grades were obtained within 24 hours of admission and before the MRI examination.

MRI Studies

All MRI studies were performed on a 1.5 T GE Genesis Signa scanner (GE Healthcare). Axial T2-weighted fast spin echo imaging was performed with the following parameters (means ± SDs from 10 randomly selected examinations): TR 3590 ± 546 msec, TE 94.9 ± 10 msec, slice thickness 3 mm, and echo train length 16 ± 4. Sagittal T2-weighted fast spin echo imaging was performed

with the following parameters: TR 3300 ± 290 msec, TE 102 ± 3 msec, slice thickness 3 mm, and echo train length 15 ± 3. For both sagittal and axial T2 imaging, the acquisition matrix was 256 × 256. The phase encoding direction was left to right for the axial sequences and craniocaudal for the sagittal sequences. The field of view ranged from 16 to 20 cm. Additional sequences performed as part of our routine trauma MRI protocol were not evaluated for the purposes of this study. An axial 2D multiecho recombined gradient echo sequence from a single normal patient was used as a control reference for identifying margins of gray matter at the upper, mid, and lower cervical levels.

Image Analysis and BASIC Scoring

Axial and sagittal T2-weighted MRI sequences were examined by a fellowship-trained neuroradiologist (J.F.T.) and a spine fellowship–trained neurosurgeon (S.S.D.), who were both blinded to the AIS grade. The epicenter of the SCI was located on the axial T2-weighted sequence and confirmed by cross-referencing with the sagittal T2-weighted sequence. A single axial image with the most severe SCI was identified for the scoring. The Brain and Spinal Injury Center (BASIC) scoring was performed according to the observations outlined in Fig. 1. Briefly, an SCI with a BASIC score of 0 represented normal spinal cord T2 relaxivity without appreciable pathological intramedullary signal. A BASIC score of 1 represented cases in which a pathological T2 hyperintensity was approximately confined to the spinal gray matter (Fig. 2). A BASIC score of 2 was assigned when a pathological intramedullary T2 hyperintensity extended beyond the margins of the central gray matter and obscured the gray-white margins, but did not involve the entire transverse extent of the spinal cord. For these cases, some peripheral normal-appearing white matter was identified. A BASIC score of 3 was assigned when the pathological T2 hyperintensity involved the entire transverse extent of the spinal cord, without any residual normal-appearing white matter. An SCI with a BASIC score of 4 was defined as a BASIC Score 3 injury with additional superimposed discrete foci of intramedullary T2 hypointensity attributed to the presence of macroscopic intramedullary hemorrhage.

The SCIs with BASIC scores of 0, 1, and 2 could be elevated by a single score if a macroscopic hemorrhage was present, although no such cases were identified in our patient cohort. For example, a BASIC score of 2 with the presence of macroscopic hemorrhage would be elevated to BASIC score of 3.

Image Processing

Digital Imaging and Communications in Medicine (DICOM) images from our university picture archiving and communication system (PACS; Agfa Healthcare) were annotated and cropped for figure production with ImageJ software (available at http://rsb.info.nih.gov/ij and developed by Wayne Rasband at NIH). We produced 3D-color surface plots of T2-weighted images with an interactive 3D-surface plot plugin for ImageJ. These surface plots were used only for figure production and were not used for primary image analysis or interrater reliability testing.

Interrater Reliability Testing Protocol

Interrater reliability was assessed by measuring the mean and SD of scores assigned by multiple raters review-

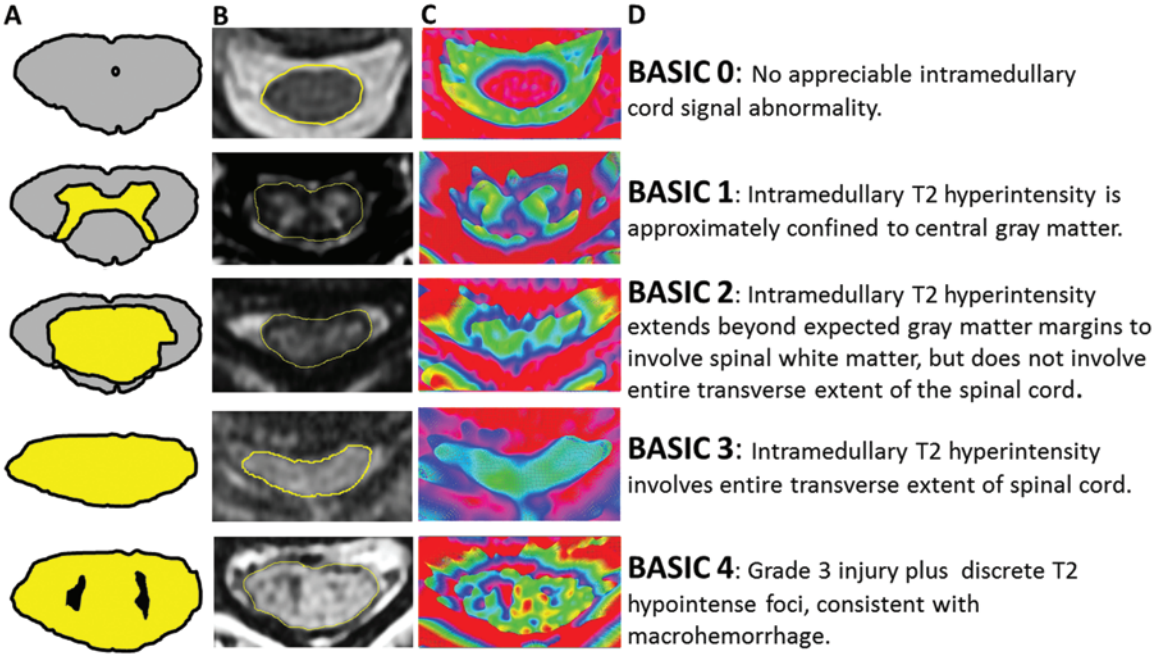

FIG. 1. The BASIC score of SCIs. Cartoon schematics **(A)**, representative axial T2-weighted MRI scans **(B)**, 3D-color surface plots based on the axial T2 image **(C)**, and brief definitions **(D)** for each of the 5 BASIC scores (ranging from 0 to 4). In the representative MRI scans **(B)**, the external contour of the spinal cord is outlined in *yellow* for better delineation. Figure is available in color online only.

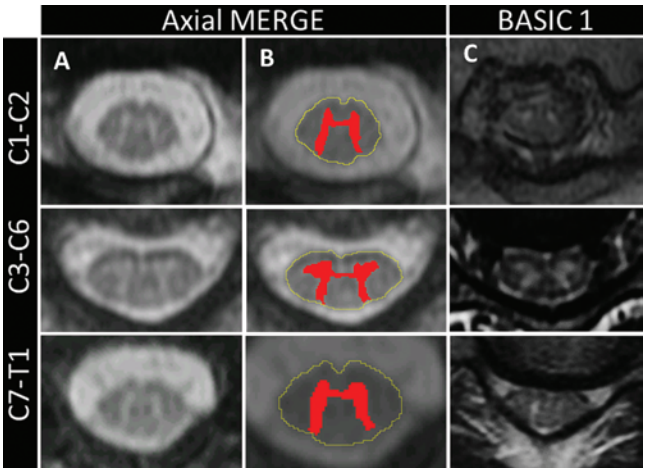

FIG. 2. Familiarity with the normal spinal cord gray matter morphology at rostral (C1–C2), middle (C3–C6), and caudal (C7–T1) cervical vertebral levels is important for rating an SCI as BASIC Score 1. **A:** Axial multi-echo recombined gradient echo (MERGE) image of the normal spinal cord clearly indicates the normal gray matter morphology at the upper, middle, and lower cervical vertebral levels. **B:** Manual segmentation of cervical spinal cord gray matter based on an axial MERGE images in A with the peripheral cord contour delineated in *yellow*. Note the large frontal horns related to the cervical enlargement at the C3–6 vertebral levels. **C:** Axial T2-weighted images from the epicenters of BASIC Score 1 SCIs at the upper, middle, and lower cervical vertebral levels. Note that the T2 hyperintensity represents the approximate boundaries of spinal cord gray matter for each cervical level. Figure is available in color online only.

ing 20 MRI studies chosen to represent all parts of the BASIC rating scale; the reliability testing was similar to that in the development of the scale established by Basso, Beattie, and Bresnahan.[2] Seven participating raters were instructed in the rating during an initial training session in which they were shown MRI studies of a range of SCIs and the method of scoring was explained. The specialties of training of the participants included neuroradiology, neurosurgery, emergency medicine, neuroanatomy, and anesthesiology. The rating of individual images was then practiced in concurrent discussions, followed by each participant silently rating the observations on the MRI studies and then comparing and discussing their scores with those of the instructors.

After the training, each rater was presented with a series of DICOM images including both the injury epicenter and adjacent normal-appearing spinal cord from 20 separate cases from our cohort with SCIs representing all levels of the BASIC scale. The cases were presented in random order. Also provided to each rater were a set of data-recording sheets, an overview of the project background and goals, a set of frequently asked questions with answers, and a score determination guide for ease of assigning scores. All participants then individually examined the 20 images and scored each of them within 20 seconds according to the descriptions provided. The data sheets were then collected, analyzed, and compared with a consensus score for each image, arrived at by the original scale developers' viewing, discussing, and arriving at the consensus score for each image. This consensus score was determined after all raters (including the experienced raters) had completed and submitted their independent ratings of the images.

Statistical Analysis

All statistical analyses were performed with a commercial software package (SPSS Inc.). Statistical correlation between the BASIC score and AIS grades at both admission and discharge were evaluated with the Pearson correlation coefficient. The differences in BASIC scores among the AIS improvement groups were analyzed with 2-tailed Student t-tests. Statistical significance was determined as $p < 0.05$.

A statistical analysis of the reliability of the BASIC classification system among different observers against the consensus scores was performed with the Kappa coefficient (κ). As described by Landis and Koch,[21] a κ of > 0.8 was interpreted as excellent reliability. The unidimensional nature of the BASIC score was assessed on all cases by all raters with exploratory factor analysis with the principal component extraction method.[29,36]

Results

Patient Characteristics

Table 1 shows the demographic and clinical characteristics of our cohort of 60 patients. Table 2 lists the complete admission and discharge AIS data for our entire cohort. All of the SCIs resulted from blunt trauma, and 17 of the patients (28%) presented with complete injury (that is, AIS Grade A). The patients were predominantly male (70%) with a mean age of 56 years (range 18–94 years) (Table 1). The most frequent injury mechanism was fall (53%), followed by motor vehicle collision (15%), bicycle accident (10%), assault (8%), pedestrian versus automobile accident (7%), and other or nonspecified mechanism (7%) (Table 1). The mean length of time between the hospital admission and the spine MRI was 8.6 ± 6 hours (range 1–39 hours). The patients were examined at the sole Level I trauma center within a dense urban catchment area where the time from injury to admission at our institution is on average less than 60 minutes. In total, 51 patients

TABLE 1. Characteristics of the patients in this study

Variable	All Patients
Total no. of patients	60
Mean age in yrs ± SD (range)	56 ± 20 (18–94)
Sex M/F (%)	42/18 (70/30)
Injury mechanism, no. of patients (%)	
Fall or jump	32 (53)
Motor vehicle collision	9 (15)
Bicycle accident	6 (10)
Assault	5 (8)
Pedestrian vs automobile accident	4 (7)
Other	4 (7)
Time to MRI in hrs ± SD (range)	8.6 ± 6 (1–39)
Mean time to discharge in days ± SD	23 ± 24

TABLE 2. The AIS grades of the 60 patients in this study at admission and at discharge

AIS Grade	No. of Patients (%)	
	Admission	Discharge
A	17 (28)	9 (15)
B	7 (12)	4 (7)
C	10 (17)	10 (17)
D	18 (30)	20 (33)
E	8 (13)	17 (28)

(85%) underwent an MRI examination within 12 hours of the hospital admission, and only 1 patient (2%) underwent the examination more than 24 hours after admission. For those patients admitted to the hospital, the average length of hospitalization was 23 days (range 4–128 days).

MRI Findings

Axial and sagittal T2-weighted MRI sequences indicated intramedullary signal abnormalities in 48 (80%) of the 60 patients. In all patients, 5 distinct patterns of intramedullary signal were identified on the axial T2-weighted sequence at the injury epicenter (Fig. 1). In 12 patients (20%), no apparent signal abnormality was observed, and their SCI finding received a BASIC score of 0. In 16 (27%) of the patients, a T2 signal hyperintensity was observed that largely conformed to the expected morphology of the central spinal gray matter; therefore, these patients' SCI was rated as BASIC Score 1. In 18 patients (30%), we observed a pattern of intramedullary T2 hyperintensity at the injury epicenter that extended beyond and obscured the expected margins of the central gray matter, but did not involve the entire transverse extent of the spinal cord on axial imaging; their injuries were therefore rated BASIC Score 2. In 9 patients (15%), an SCI resulting in diffuse intramedullary T2 hyperintensity that involved the transverse extent of the cord was rated as BASIC Score 3. The remaining 5 patients (8%) had SCIs that resulted in diffuse T2 hyperintensity with superimposed discrete foci of T2 hypointensity, consistent with intramedullary hemorrhage, and their SCI severities were rated as BASIC Score 4. None of the patients showed evidence for macroscopic hemorrhage in the absence of diffuse transverse T2 hyperintensity.

BASIC Score Strongly Correlates With Admission AIS Grade

We observed a highly significant correlation between the AIS grade at the time of admission and the morphological pattern of intramedullary signal abnormality as rated by the BASIC score on the admission MRI study. Figure 3 graphically displays the linear correlation between the AIS grade and the BASIC score at admission. Along the severe spectrum of an acute SCI, a BASIC score of 3 or 4 was nearly always associated with an admission AIS grade of A, that is, in 13 (76%) of the 17 patients with an admission AIS Grade A. Among the 43 patients with an AIS grade less severe than A, only 1 patient (2%) had

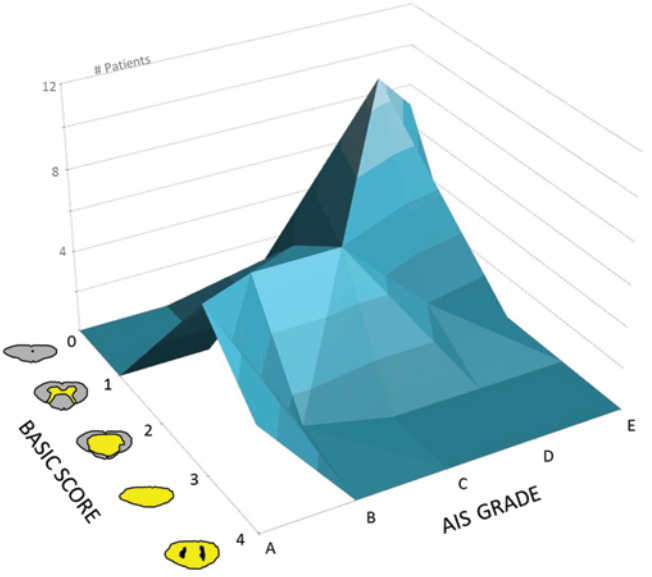

FIG. 3. A 3D surface plot indicates a strong correlation of the BASIC score with the AIS grade at the time of hospital admission (Pearson coefficient = –0.877, $p = 4.0 \times 10^{-20}$). The height of the surface plot (that is, the z-axis) corresponds to the number of patients with corresponding BASIC scores and AIS grades within our cohort. Note the course of the peak of the surface plot clearly tracing the strong linear correlation between the BASIC score and the AIS grade. Figure is available in color online only.

a BASIC score of 3, and none had a BASIC score of 4. A BASIC score of 4 was always observed with an SCI rated as AIS Grade A at admission. Thus, a high BASIC score, that is, of 3 or 4, was specific for severe injury at admission.

On the mild end of the SCI severity spectrum, an SCI with a BASIC score of 1 or 0 was never observed in patients with an AIS grade of A or B on admission. A BASIC score of 0 (that is, a normal cord signal) was entirely limited to patients with an admission AIS grade of D or E.

BASIC Score Strongly Correlates With AIS Grade at Discharge

The correlation between the AIS grade at the time of discharge and the BASIC score based on the morphological pattern of intramedullary signal abnormality on the admission MRI study was also highly significant. Figure 4 displays the linear correlation between the admission AIS grade at discharge and the BASIC score. Figure 5 shows a plot of the admission and discharge AIS grades for all patients stratified by the 5 BASIC score groups. Of 12 patients with an SCI rated as BASIC Score 0, 11 (92%) were discharged with an AIS Grade E, with the remaining single patient discharged with AIS Grade D. All 16 patients with a BASIC score of 1 were discharged with an AIS grade of D or E. Of 18 patients with a BASIC score of 2, 16 (88%) were discharged with an AIS grade of C or D. Among 9 patients with a BASIC score of 3, 6 (67%) were discharged with an AIS grade of A or B. All 4 patients with a BASIC score of 4 were discharged with an AIS grade of A.

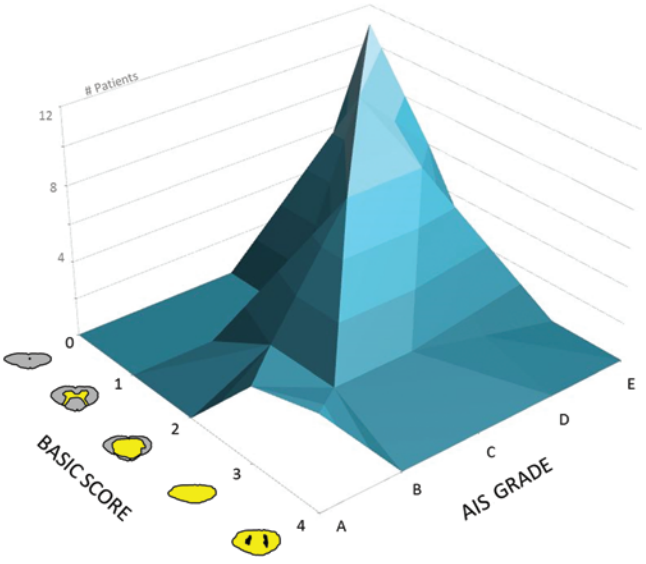

FIG. 4. A 3D surface plot indicates a strong correlation between the BASIC score and the AIS grade at the time of hospital discharge (Pearson coefficient = –0.880, $p = 2.0 \times 10^{-20}$). The height of the surface plot (that is, the z-axis) corresponds to the number of patients with corresponding BASIC scores and AIS grades within our cohort. Note the course of the peak of the surface plot clearly tracing the strong linear correlation between the BASIC score and the AIS grade. Figure is available in color online only.

BASIC Score Distinguishes Patients With an Admission AIS Grade of A Who Improve at Discharge

At the time of discharge, 8 (47%) of the 17 patients with an admission AIS grade of A improved by at least one AIS grade. The BASIC scores among AIS Grade A patients whose condition did not improve were significantly higher than among those who did improve by at least one AIS grade (3.6 ± 0.5 vs 2.6 ± 0.5, respectively, $p < 0.01$; Fig. 6).

BASIC Score and Interobserver Reliability

The mean and median κ scores for all raters were 0.83 and 0.81, respectively (both $p < 0.00001$), relative to the consensus score, consistent with excellent reliability and reproducibility. A factor analysis with principal component analysis indicated that the BASIC score represented a unidimensional outcome, with high correspondence among the 7 raters (Table 3 and Fig. 7).

Discussion

In the present study, we sought to classify the severity of an acute SCI according to the transverse extent of signal abnormalities as qualitatively assessed on a single axial T2-weighted MR image centered at the lesion epicenter. Specifically, we introduce a 5-point (ranging from 0 to 4) ordinal classification system, which encompasses the spectrum of SCI severity, from a normal-appearing spinal cord to a diffusely abnormal cord signal hyperintensity with superimposed macroscopic intramedullary hemorrhage (Fig. 1). We excluded cord transection injuries from consideration because of the distinct and easily distinguished imaging pattern associated with this SCI type. The proposed BASIC score builds on previously described MRI-based systems for classifying acute traumatic SCIs, and in our analyses it strongly correlated with AIS grades at the hospital admission for the SCI and at discharge (Figs. 3 and 4). Moreover, the BASIC score stratifies the SCIs on the basis of the anatomically and functionally relevant extent of transverse injury. It may help identify those patients who present with the most severe clinical injury (that is, with AIS Grade A) and who will improve by at least one AIS grade by the time of discharge (Fig. 6).

Both human and animal studies have demonstrated that the transverse extent of an SCI and relative white matter sparing are major determinants of functional outcomes.[5,6,16,18,22] To our knowledge, the present study is the first to correlate clinical symptoms and outcomes with the

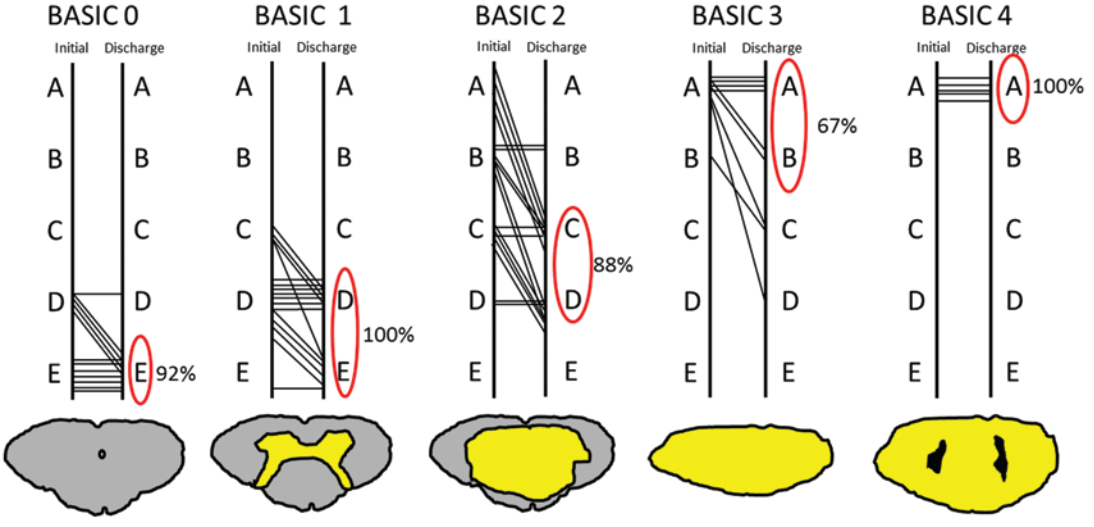

FIG. 5. Admission and discharge AIS grades for all patients in our cohort are plotted within each BASIC score group, with a cartoon schematic of the SCI below each plot. The percentages of patients within each BASIC group with a discharge AIS grade circled in *red* are listed to the right of the discharge AIS grades. Figure is available in color online only.

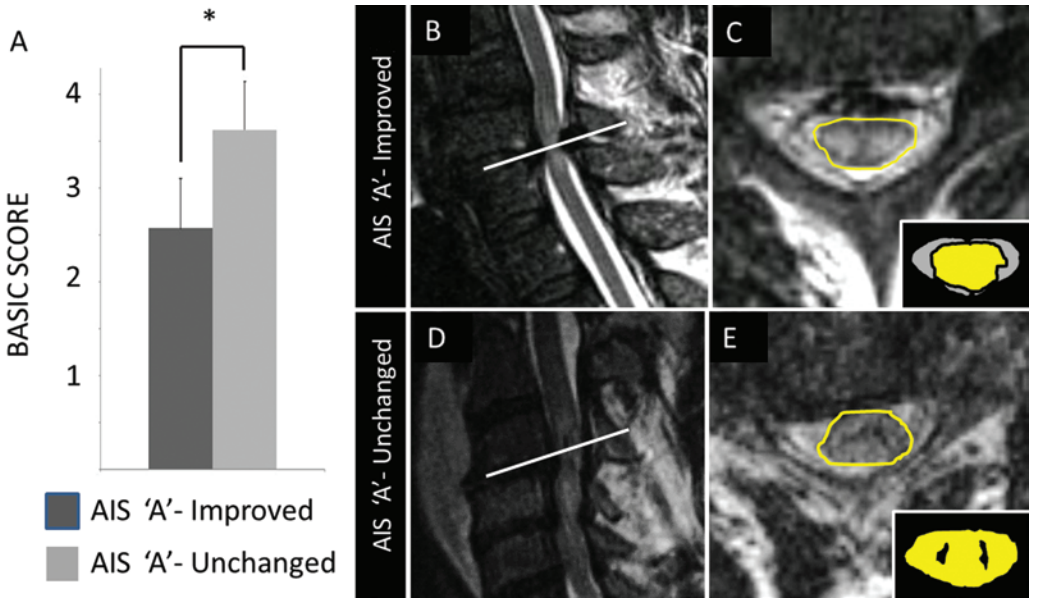

FIG. 6. The BASIC scores for patients who presented with complete injury (that is, with AIS Grade A) and who improved by at least one AIS grade are significantly lower than those for AIS Grade A patients whose SCI showed no improvement. The bar graph shows a significantly lower BASIC score for patients with AIS Grade A whose injury improved in AIS grade by the time of follow-up compared with AIS Grade A patients whose injuries did not improve ($p < 0.01$) **(A)**; *error bars* indicate the SD. Sagittal **(B)** and axial **(C)** T2-weighted images from a patient with an SCI sustained in a fall and presenting with AIS Grade A indicate abnormal intramedullary T2 hyperintensity with a pattern of T2 signal abnormality on the axial image at the injury epicenter **(B)** consistent with a BASIC score of 2 (see schematic **inset** in the right lower corner). This patient's condition improved to AIS Grade C at the follow-up. Sagittal **(D)** and axial **(E)** T2-weighted images from a patient with an SCI injury due to an assault and also presenting with AIS Grade A show abnormal intramedullary T2 signal at the injury epicenter **(D)** consistent with a BASIC score of 4 (see schematic **inset** in the right lower corner). This patient did not recover from the SCI at the time of follow-up. White lines in B and D approximate the level of the axial T2 image for each patient. For better delineation, the peripheral margins of the spinal cord are outlined in yellow in C and E. Figure is available in color online only.

transverse extent of MRI T2 signal abnormality in the axial plane in humans. Rather than arbitrary measurements of the longitudinal extent of signal abnormality in the sagittal plane, axial imaging enables the definition of anatomically relevant spinal involvement in a graded manner. With an SCI severity rated as BASIC Score 1, T2 hyperintensity is approximately confined to the spinal gray matter. The relatively good clinical outcomes at discharge for patients with a BASIC score of 1 in our study (all of these patients were discharged with an AIS grade of D or E) suggest such signal abnormality does not reflect significant coagulative necrosis or irreversible frontal horn disruption, but more likely represents vasogenic edema, as has been suggested by other authors.[9,31]

When a T2 hyperintense signal extended beyond the approximate confines of gray matter (that is, in patients with BASIC scores of 2–4), patients had a worse prognosis (Fig. 5). Importantly, distinguishing patients who have some spared white matter signal (a BASIC score of 2) from those with diffuse transverse T2 hyperintensity (a BASIC score of 3) allows for identifying those patients whose SCIs would all be classified as having multilevel hyperintensity according to previous sagittal T2 signal grading systems.[4] Our observations of a functionally relevant distinction between SCIs rated as BASIC Score 2 or 3 are consistent with preclinical data, and this corroboration highlights the important role of spared white matter in predicting outcomes.[6,17,18,22] In our cohort, patients with a BASIC score of 2 fared better than those with a BASIC score of 3, with 88% of BASIC Score 2 patients achieving an AIS grade of C or D and no AIS Grade A at discharge, as opposed to 67% of BASIC Score 3 patients discharged with AIS Grade A or B (Fig. 5).

Consistent with results based on previous classification systems,[3,12,24,27] the presence of macroscopic intramedullary hemorrhages in our cohort predicted a poor prognosis. All of the patients with a BASIC score of 4 were

TABLE 3. Principal component analysis of the BASIC score for each rater and the consensus

Rater No.	Principal Component 1
1	0.966
2	0.988
3	0.769
4	0.971
5	0.845
6	0.915
7	0.947
Consensus score*	0.988

* The consensus score of 20 images used for the interrater testing was collaboratively arrived at by the 2 developers of the BASIC score scale.

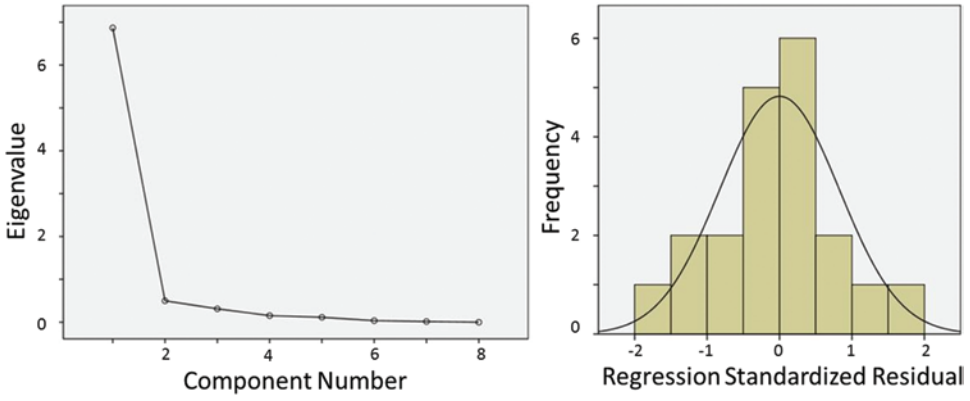

FIG. 7. Left: A screen plot of factor analysis (via principal component analysis extraction) on all ratings, indicating that the BASIC scores for SCIs reflect a unidimensional linear metric characterized by a single principal component with an eigenvalue of > 1. **Right:** A principal-component loading matrix indicating that all raters' scores as well as the consensus score loaded very highly onto the BASIC score unidimensional factor (that is, on Principal Component 1). The frequency of residual errors relative to the consensus scores was normally distributed, indicating that novice ratings, on average, strongly and linearly correlated with the expert consensus rating, with only a small number of normally distributed random errors. Together, these results suggest that the BASIC score has high interrater reliability and good parametric properties (see also Table 3). Figure is available in color online only.

discharged with an unchanged AIS Grade A. Of note, we did not use gradient- or susceptibility-weighted sequences, which have demonstrated increased sensitivity to intramedullary blood products.[40] Further studies are required to evaluate the prognostic value of these more sensitive susceptibility-weighted sequences. Importantly, not all of the patients presenting with AIS Grade A had evidence of macroscopic hemorrhage or diffuse axial T2 hyperintensity. We observed that some patients who presented clinically with complete injury had BASIC scores that suggested a less severe injury (Fig. 6).

Less severe BASIC scores were more commonly observed in those patients with AIS Grade A SCIs that improved by at least one AIS grade by the time of discharge. Thus, the BASIC score discriminated between AIS Grade A patients at presentation whose condition improved by at least one AIS grade by the time of discharge, and those who showed no improvement as assessed by the AIS grading (Fig. 6). While longer-term follow-up and prospective data are needed to corroborate these preliminary results, the present data suggest that the BASIC score may be very helpful in identifying those patients who are the best candidates for clinical trials of experimental higher-risk invasive procedures such as intramedullary injection of stem cells or devices.

The slightly older demographic of the patients in our cohort differs from the typical demographics reported for patients with acute traumatic SCIs.[7,34] This shift represents a trend we have observed for all SCIs at our institution, with an older second peak in SCI patients after a fall. This appears to reflect the specific population demographic of the San Francisco Bay area. Similar trends have been recently reported in the Canadian population.[39] Although a demographic subgroup analysis was not performed, no notable differences in patterns of transverse intramedullary T2 signal hyperintensity among age group or injury mechanisms were observed. However, to validate the BASIC score, future studies including larger patient populations across geographic regions are warranted.

Limitations

There are limitations to the current study, including its retrospective design, variable timing of the acute-phase MRI, and a relatively short clinical follow-up. In addition, interrater reliability testing was not performed directly at a PACS station but rather in a group setting with presentation of index images selected by a neuroradiologist from the injury epicenter and from normal spinal cord. In our opinion, it is in fact easier to assign a BASIC score by scrolling through the axial and sagittal MRI studies on a dedicated PACS station, as is the typical practice followed by most spine surgeons and radiologists. Prospective validation studies with long-term follow-up are planned to validate these preliminary data. An additional limitation is the subjectivity of our classification system. Although qualitative and subjective in nature, the BASIC score scale demonstrated excellent interrater reliability (mean κ score = 0.83) across observers with varied expertise. Moreover, it can be performed rapidly without performing manual measurements or time-consuming image postprocessing. Axial T2-weighted imaging is routinely performed as part of MRI protocols for cervical spine trauma and as a recommended sequence for acute spinal cord MRI protocols according to the SCI Common Data Elements of the National Institute of Neurological Disorders and Stroke (NINDS). Therefore, a modification of existing protocols is not required. One limitation of T2 signal–based MRI classification systems such as BASIC for SCI evaluation is the nonspecific nature of the T2 signal hyperintensity. This probably contributes, at least in part, to some of the variable clinical outcomes we observed in patients within each BASIC score group (Fig. 5).

Changes in T2 signals also depend on the timing of the MRI after an injury.[23,26,28,38] Although we excluded all patients who underwent an MRI examination more than 48 hours after admission and even though 85% of our patients had MRI within 12 hours of admission, the variable timing of the MRI examination within our selected time interval

also probably influenced the patterns of observed T2 signal abnormality in the setting of a rapidly evolving acute SCI. Further studies evaluating the optimal timing of MRI examinations for prognostic purposes during the acute phase of SCI are needed. Despite these limitations and when compared with previous classification systems[3,4,12,35] on which it is built, the BASIC score has excellent prognostic capability, particularly for patients with intermediate injury severity. Advanced MRI techniques, including diffusion tensor imaging, magnetization transfer imaging, MR spectroscopy, and functional MRI have shown varying potentials as noninvasive functional biomarkers for SCI.[37,41] The prognostic superiority of these techniques to standard T2-weighted imaging will need to be established before their routine clinical implementation. The BASIC score for SCIs may represent one standard for such future comparisons.

Conclusions

We present a novel, simple, and reliable classification system for grading acute blunt traumatic SCIs on the basis of the pattern of T2 signal abnormality as assessed in the axial plane at the injury epicenter. The BASIC scale has excellent prognostic potential across all SCI severities. These preliminary data suggest that the BASIC score will help distinguish patients who present with an AIS Grade A that improves before discharge from those who will not recover significant function. The proposed classification system builds on the previous literature and may provide prognostic stratification of patients with SCIs by reflecting functionally and anatomically significant patterns of T2 hyperintensity in the axial plane, which is not dependent on arbitrary measures of longitudinal signal abnormality. Future prospective and well-controlled studies are needed to further validate the prognostic value of the BASIC score.

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Author Contributions

Conception and design: Dhall, Talbott. Acquisition of data: Dhall, Talbott, Whetstone, Readdy. Analysis and interpretation of data: Dhall, Readdy, Mabray. Drafting the article: Talbott. Critically revising the article: Dhall, Whetstone, Ferguson, Bresnahan, Beattie, Pan, Manley. Reviewed submitted version of manuscript: Bresnahan, Beattie, Pan, Manley, Saigal, Hawryluk. Statistical analysis: Ferguson. Study supervision: Dhall.

Correspondence

Sanjay S. Dhall, Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Ave., Rm. M-779, San Francisco, CA 94143. email: sanjay.dhall@ucsf.edu.

OPEN

Spinal Cord (2017) 55, 559–565
Official journal of the International Spinal Cord Society
www.nature.com/sc

ORIGINAL ARTICLE

Pulmonary outcomes following specialized respiratory management for acute cervical spinal cord injury: a retrospective analysis

EC Zakrasek[1], JL Nielson[2], JJ Kosarchuk[3], JD Crew[1,3], AR Ferguson[2,4] and SL McKenna[3,5]

Study design: Retrospective analysis.
Objectives: To identify multivariate interactions of respiratory function that are sensitive to spinal cord injury level and pharmacological treatment to promote strategies that increase successful liberation from mechanical ventilation.
Setting: United States regional spinal cord injury (SCI) treatment center.
Methods: Retrospective chart review of patients consecutively admitted to Santa Clara Valley Medical Center between May 2013 and December 2014 for ventilator weaning with C1–C5 American Spinal Injury Association Impairment Scale (AIS) A or B SCI, <3 months from injury and who had a tracheostomy in place. A nonlinear, categorical principal component analysis (NL-PCA) was performed to test the multivariate interaction of respiratory outcomes from patients ($N=36$) being weaned off ventilator support after acute SCI with ($N=15$) or without ($N=21$) theophylline treatment.
Results: In total, 36 patients met inclusion criteria (2 C1, 5 C2, 11 C3, 14 C4 and 4 C5). The NL-PCA returned three independent components that accounted for 95% of the variance in the data set. Multivariate general linear models hypothesis tests revealed a significant syndromic interaction between theophylline treatment and SCI level (Wilks' Lambda, $P=0.028$, F (12,64) = 2.116, $\eta^2=0.256$, $1-\beta=0.838$), with *post hoc* testing demonstrating a significant interaction on PC1, explained by a positive correlation between improved forced vital capacity and time it took to reach 16 h of ventilator-free breathing. Thirty-three patients (92%) achieved 16 h of ventilator-free breathing (VFB) and 30 patients (83%) achieved 24 h of VFB.
Conclusions: We suspect that some portion of the high success rate of ventilator weaning may be attributable to theophylline use in higher cervical SCI, in addition to our aggressive regimen of high volume ventilation, medication optimization and pulmonary toilet (positive pressure treatments and mechanical insufflation–exsufflation).
Spinal Cord (2017) **55,** 559–565; doi:10.1038/sc.2017.10; published online 21 February 2017

INTRODUCTION

Respiratory dysfunction remains a leading cause of morbidity and mortality after spinal cord injury (SCI).[1–3] The pathophysiology of respiratory dysfunction in SCI is multifactorial, resulting from diaphragmatic weakness, accessory muscle weakness, impaired cough, decreased surfactant production and unopposed vagal tone leading to increased secretions and bronchospasm.[1] The greatest determinant of respiratory failure after acute SCI is the level and completeness of injury relative to the phrenic nucleus at C3–C5.[3,4] Indeed, diaphragmatic function is responsible for 65% of an individual's forced vital capacity.[4] Although there have been promising results with phrenic nerve and diaphragm motor-point stimulation,[5] mechanical ventilation remains the mainstay of management for patients with respiratory failure after SCI. At the time of discharge from acute hospitalization, greater than 70% of patients with complete cervical SCI at C5 and above have historically been shown to require ongoing mechanical ventilation.[6] Unfortunately, mechanical ventilation is one of the most costly consequences of cervical SCI due to the associated infectious risks, social isolation and financial and caregiver burdens.[1,4,7]

Methylxanthines such as theophylline have been used in respiratory dysfunction since the 1920s.[8] The earliest published use of methylxanthines for respiratory dysfunction in SCI was about 40 years later.[9] Theophylline has three primary modes of action in the treatment of pulmonary dysfunction including bronchodilation, anti-inflammation and improved diaphragmatic contractility.[10–12] In cervical SCI, theophylline has an additional proposed mechanism of improving pulmonary function, namely activation of a latent crossed phrenic pathway by adenosine receptor antagonism.[13] Despite multiple promising animal studies exploring the use of theophylline in upper cervical SCI,[1,13–15] human studies in SCI are limited to case reports and one placebo-controlled study of theophylline use in chronic, non-ventilator-dependent SCI where no significant benefit was observed.[16–18]

[1]Department of Orthopedic Surgery, Stanford Hospitals and Clinics, Palo Alto, CA, USA; [2]Brain and Spinal Injury Center, Zuckerberg San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, USA; [3]Department of Physical Medicine and Rehabilitation, Santa Clara Valley Medical Center, San Jose, CA, USA; [4]San Francisco VA Medical Center, San Francisco, CA, USA and [5]Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA
Correspondence: Dr SL McKenna, Director of Rehabilitation Trauma Center, Department of Physical Medicine and Rehabilitation, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128, USA.
E-mail: Stephen.Mckenna@hhs.sccgov.org
Received 20 March 2016; revised 29 December 2016; accepted 5 January 2017; published online 21 February 2017

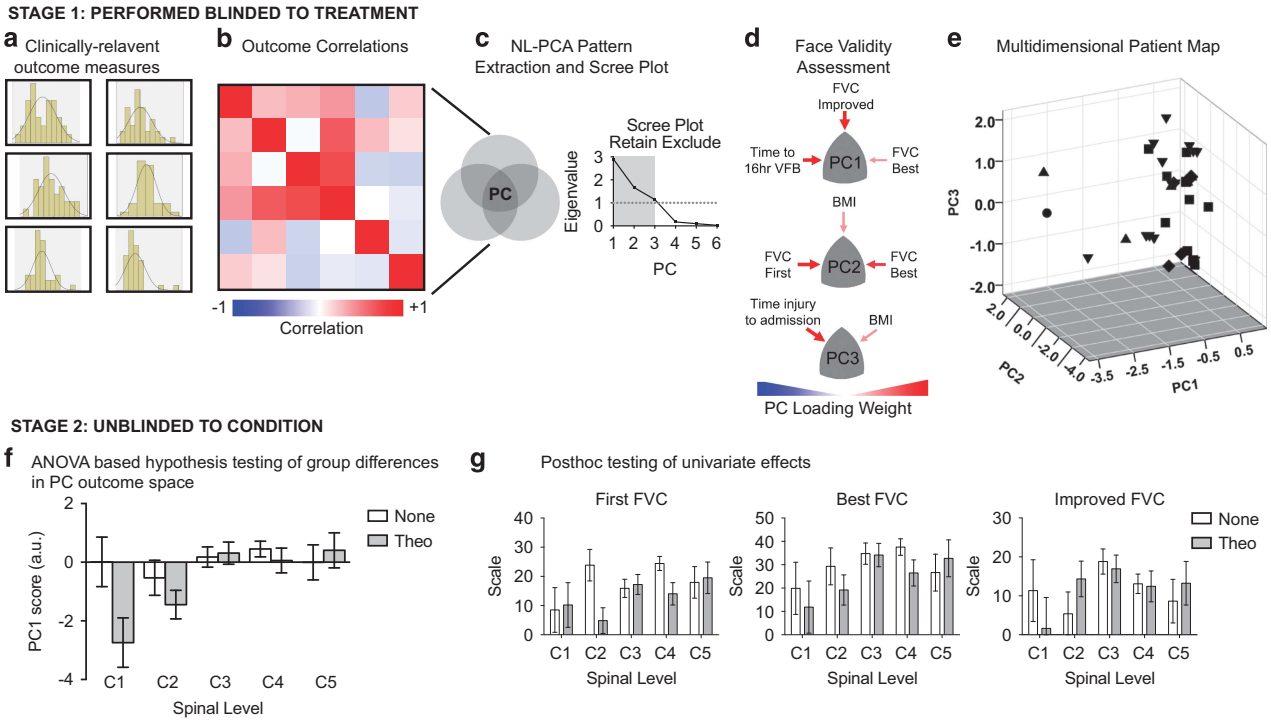


Figure 1 Statistical analysis workflow. (**a**) Data distribution of each clinically relevant outcome was assessed to determine the type of statistical tests to use. (**b**) Correlation matrix of all outcomes used to perform (**c**) nonlinear principal component analysis (NL-PCA) to identify three principal components (PC) based on both having eigenvalues greater than 1 whose (**d**) multivariate outcomes also had face validity to the clinicians who collected the data. (**e**) Composite PC scores from each multivariate outcome was assigned to each patient and used to map each subject into a three-dimensional space based on their syndromic outcomes generated with NL-PCA. Workflows **a**–**e** were all conducted blinded to treatment condition. (**f**) Hypothesis testing was performed on multivariate outcomes (PC1–PC3) for interactions between type of treatment (group 1 vs group 2) and SCI spinal level on the multivariate space. (**g**) Individual outcomes tested with the same hypothesis using univariate statistics, demonstrating that only the multivariate outcomes are sufficiently powered for hypothesis testing, whereas individual outcomes separately cannot reliably test these hypotheses.

In a previous publication from our SCI center, we demonstrated a comprehensive and effective pulmonary management strategy for acute cervical SCI that uses a combination of high tidal volume ventilation, high-frequency percussive ventilation and mechanical insufflation–exsufflation techniques.[3] In the years since this publication, we have continued to optimize our pulmonary toilet and ventilator weaning protocols with the hope of giving our patients the best chance of enjoying a life of ventilator independence. One of the more recent additions to our protocol is the routine administration of oral theophylline during ventilator weaning. The following retrospective chart review represents an updated description of clinically important respiratory outcomes in patients with ventilator-dependent tetraplegia admitted to the Rehabilitation Trauma Center, a multidisciplinary acute SCI medicine unit in our center under the co-management of Neurocritical Care and Physiatry. We sought to test the interaction between theophylline treatment and SCI level on the multidimensional correlation of different measures of respiratory function and health to identify treatment options that will decrease the time it takes to wean patients off a mechanical ventilator.

PATIENTS AND METHODS

Participants

After obtaining approval by our center's Institutional Review Board, we performed a retrospective chart analysis of consecutively admitted SCI patients to the Rehabilitation Trauma Center between May 2013 and November 2014. We included all traumatic spinal cord-injured patients with the following: neurologic level of injury between C1 and C5, American Spinal Injury Association Impairment Scale (AIS) A or B, date of injury within 3 months of admission, history of tracheostomy and ventilator dependence. We excluded patients who had already maintained 16 or more hours of ventilator-free breathing (VFB) at the time of admission. We documented basic demographics as well as pulmonary comorbidities such as smoking, asthma, chronic obstructive pulmonary disease, congestive heart failure, lung trauma at the time of SCI and obstructive sleep apnea. Patients were defined as having received a course of theophylline if they were treated with at least 7 consecutive days of oral theophylline during their stay.

Outcomes

We evaluated two clinically important primary outcomes including (i) the ability to wean off the ventilator for all waking hours (16 h of VFB) and (ii) complete liberation from the ventilator (24 h of VFB). We examined secondary outcomes including time from injury to first attempt to breathe without ventilator support (initiation of VFB), time from injury to 16 h of VFB, time from injury to 24 h of VFB, time from injury to decannulation and change in forced vital capacity (FVC) during admission (defined as the best FVC minus the first FVC; 'first FVC' was defined as the best FVC recording during the first week of admission given inconsistency of initial FVCs; 'best FVC' was defined as the 95th percentile of all FVCs collected during the patient's stay in order to exclude outliers). For statistical analysis, FVCs were normalized to cubic centimeter per kilogram of ideal body weight. As normal lung volumes are predicted on the basis of sex and height, ideal body weight for male patients was calculated using the formula 50+0.91 (centimeters of height—152.4), and for female patients the formula was 45.5+0.91 (centimeters of height—152.4).[19]

Table 1 Patient demographics

	N *(%)*
Gender	
Male	29 (81)
Female	7 (19)
Age	
16–30 y	11 (31)
31–45 y	13 (36)
46–60 y	8 (22)
61–75 y	2 (6)
>75 y	2 (6)
Mechanism of injury	
Transport	18 (50)
Fall	8 (22)
Sports	5 (14)
Violence	5 (14)
Level of injury	
C1	2 (6)
C2	5 (14)
C3	11 (31)
C4	14 (39)
C5	4 (11)
Impairment Scale	
A	30 (83)
B	6 (17)

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height measured in meters.

A respiratory therapist obtained forced vital capacities daily or twice daily. Forced vital capacity was measured by the use of a Wright Spirometer unless patients were in isolation in which case a disposable spirometer kit was used. The disposable spirometer consists of a 5-liter calibrated bag, which can be used with either mouthpiece or tracheostomy. A prior internal clinical analysis of patients in isolation showed that correction of our disposable spirometer bag values by a factor of 2/3 correlated with the Wright Spirometer values, and thus adjusted values were used for patients in isolation. Finally, we documented any adverse effects that could be attributed to theophylline administration.

Statistical plan

Because of the complex nature of SCI pathophysiology, we recognize that any single outcome will not be sufficiently powered in small patient populations to detect strong effect sizes. Knowing that univariate approaches will not fully tap into the interplay between different measures of dysfunction that are inherent in such a complex disorder, we developed an analytical workflow according to methods that have been optimized to capture the heterogeneity of this disorder.[20–23] A set of physiologically meaningful outcomes were determined by the clinicians collecting the data, including BMI, first FVC, improved FVC, best FVC, time to admission and 16 h of VFB (Figure 1a). Using these variables, a nonlinear, categorical principal component analysis (NL-PCA) was applied to the data (Figures 1b and c) to determine which variables clustered together as well as their contributions to overall outcome variance. Each variable was analyzed as a categorical/ordinal measure, and a three-factor structure was imposed on the SCI syndromic space.[20,23] Upon examining the three components, although parsimonious, they were not easily interpretable. A varimax rotation was performed by first optimally scaling the variables using NL-PCA, and then rotating the resulting factors, using linear PCA. To evaluate the stability of results given the relatively small *N*, bootstrapping was conducted by repeating the NL-PCA analysis 1000 times while randomly dropping 20% of the sample to simulate a larger population. Thus, the three-component NL-PCA with varimax rotation was considered parsimonious and interpretable (Figure 1d). Once we validated the components and found them to have clinically relevant face validity, (all done blinded to treatment), we then performed hypothesis testing on the three-dimensional PC outcome space (Figure 1e), blocking groups of patients based on SCI spinal level (C1–C5) and treatment condition (theophylline or nothing). Multivariate general linear model was used for hypothesis testing on each set of PC scores (PC1–PC3), to test whether treatment and/or SCI level of injury significantly impacted each of the three multivariate outcomes generated using NL-PCA (Figure 1f). The final wave of analyses involved *post hoc* testing on the univariate outcomes individually (Figure 1g). Our test for normal distribution failed both the Kolmogorov–Smirnov and Shapiro–Wilk tests for normality; so we used nonparametric tests for hypothesis testing.

The Pearson chi-square test was used to determine whether there was a significant difference between categorical variables. For continuous variables, the Mann–Whitney *U*-test was used.

Statistical Package of Social Science (SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. Histogram plots were generated using GraphPad Prism (v 7.0a) and three-dimensional plots of PC syndromic space were generated using SPSS syntax. Overview of the statistical analysis workflow is depicted in Figure 1. Statistical significance was evaluated at a threshold of $P<0.05$. Significant PC loadings were set to a threshold of |0.4|, based on the threshold of the PC loading, which is the same as a Pearson correlation, where the *r* value necessary to detect significant correlations ($P<0.05$) depends on the degrees of freedom (df) in the data set (N-2). The value of the loadings needed to detect significance with df = 34 is |0.35| or higher, according to the Table of Critical Values for Pearson's *r*, and is therefore sufficient for the current study.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Table 2 Ventilator weaning outcomes

Level of injury (n)	*16 h VFB*		*24 h VFB*		*Decannulated*	
	N	%	N	%	N	%
C1 (2)	1	50	0	0	0	0
C2 (5)	3	60	2	40	1	20
C3 (11)	11	100	10	91	7	64
C4 (14)	14	100	14	100	13	93
C5 (4)	4	100	4	100	3	75

Abbreviation: VFB, ventilator-free breathing.

Statement of ethics

The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

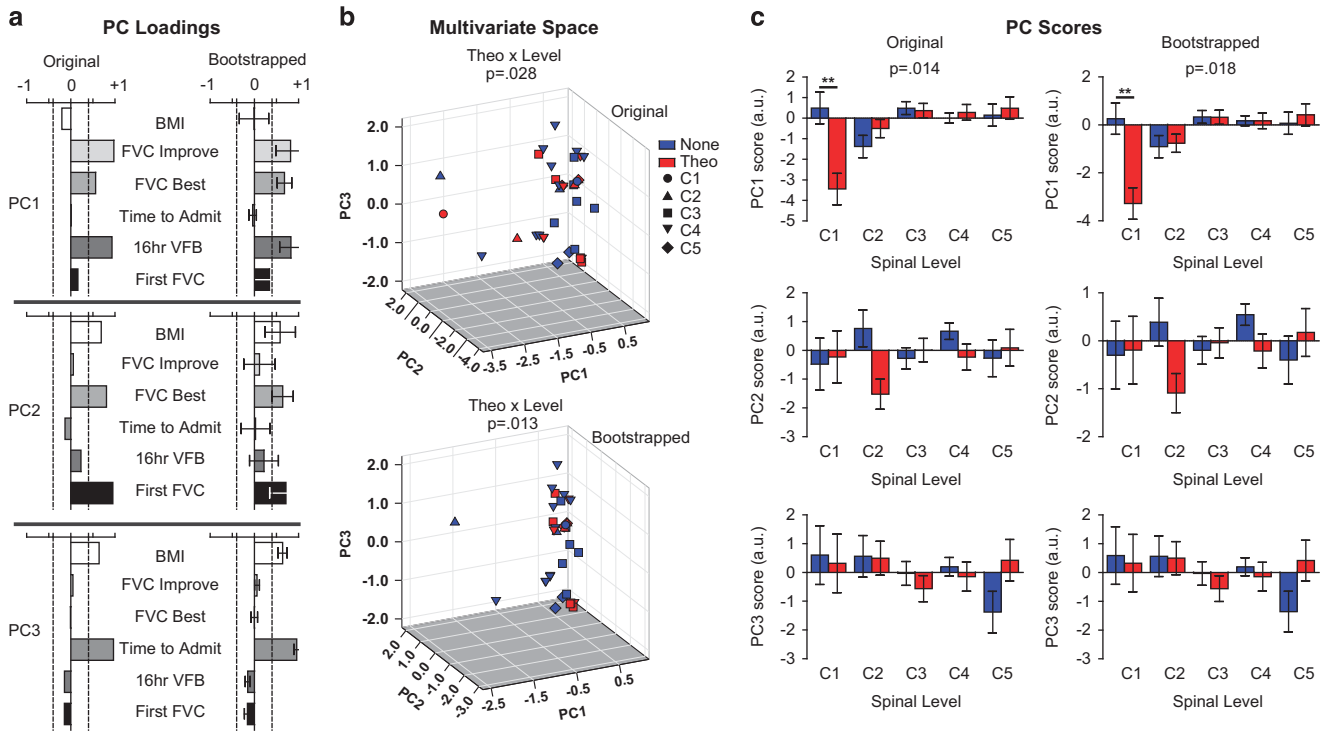
RESULTS

Patient clinical characteristics

A total of 40 patients with C1–C5 AIS A or B SCI were admitted during the study period; however, four patients were excluded for having already appropriately weaned off the ventilator by sustaining ⩾16 h per day of VFB before admission. Patient demographics can be seen in Table 1.

Mean time from injury to admission to the Rehabilitation Trauma Center was 28 days (median 25.5, range 3–54 days). Mean time to initiation of VFB from admission to the Rehabilitation Trauma Center was 7.7 days (median 3, range 1–43 days). Mean FVC on admission was 1180 ± 634cc (mean ± s.d., median 1042 cc) and adjusted for ideal body weight 17.7 ± 8.8 cc kg^{-1}, (median 16.6cc kg^{-1}).

Rates of successful VFB are presented in Table 2.



Counts	Spinal Level					Total
	C1	C2	C3	C4	C5	
None	1	2	6	10	2	21
Theophylline	1	3	5	4	2	15
Total	2	5	11	14	4	36

Figure 2 Multivariate effects of theophylline treatment on respiratory function. (**a**) NL-PCA (original) and stability testing (bootstrapped) of respiratory outcome patterns revealed a three-factor structure that accounted for 95% of the variance in the data set. Principal component 1 (PC1) accounted for 48.3% of the variance in the data set, and represents the positive correlation between FVC best, FVC improved and time to 16 h of VFB. After bootstrapping the sample, the error range of PC1 remained above a PC loading of 0.4 (vertical dotted lines), suggesting a stable relationship between these three variables. PC2 accounted for 27.8% of the variance in the data set, and represents the positive correlation between BMI, FVC first and FVC best. Bootstrapping the sample revealed error variance in the PC loadings that fell below 0.4 for BMI and first FVC, with only best FVC remaining stable. PC3 accounted for 19.0% of the variance in the data set, and represents the positive correlation between BMI and time from injury to admission, which remained stable after bootstrapping. (**b**) Multivariate hypothesis testing of PC scores for each patient (individual dots) identified a significant interaction between theophylline treatment (red color) and SCI level (different shapes) across the full three-dimensional syndromic space that was stable after bootstrapping. (**c**) *Post hoc* hypothesis testing for each principal component (PC) showed a significant interaction between treatment and SCI level on PC1.

Multivariate analysis of health and respiratory function

To explore the multidimensional impact of theophylline treatment on these patients, we performed NL-PCA on respiratory outcomes from patients ($N=36$) attempting to be weaned off a ventilator after acute SCI with ($N=15$) or without ($N=21$) theophylline treatment (Figure 2). Varimax rotation of NL-PCA loadings revealed the presence of strong loadings on each of the three components (Figure 1d). The PC loadings can be seen in the left column of Figure 2a with bootstrap-estimated variances shown in the right column. The resulting PC scores for each patient, both from the original analysis and the bootstrapped analysis, were used to create the three-dimensional space shown in Figure 2b. Bootstrapping this data to evaluate stability (top right graphic in Figure 2c) did not show substantial wobble in the results.

NL-PC scores were assigned to each patient to test the hypotheses about treatment group and injury SCI level on multidimensional outcomes of respiratory function, based on the time between injury to admission at Santa Clara Valley Medical Center, time to 16 h of VFB, FVC (measured as first assessment, best assessment and improvement) and BMI. Multivariate general linear models were used to test for significance of treatment and SCI level on each PC. NL-PCA returned three independent components with eigenvalues greater than 1 (Figure 1c) that accounted for 95% of the variance in the data set. PC1 accounted for 48.3% of the variance in the data set, with an eigenvalue of 2.90. Loadings indicate that PC1 represents the positive cross-correlation between best FVC, improvement in FVC and time to 16 h of VFB (Figure 2a, top panel, original, PC1). After bootstrapping the sample, the error range of PC1 remained above a PC loading of 0.4, suggesting that it reflects a stable multidimensional outcome metric (Figure 2a, top panel, bootstrapped, PC1). Based on this, we have named PC1 as improved vital capacity and latency to ventilator weaning. PC2 accounted for 27.8% of the variance in the data set, with an eigenvalue of 1.67, and represents the positive correlation between BMI, first FVC and best FVC (Figure 2a, middle panel, original, PC2). Bootstrapping the sample revealed error variance in the PC loadings that fell below 0.4 for BMI and first FVC, with only best FVC remaining stable (Figure 2a, middle panel, bootstrapped, PC2). Based on this, we have named PC2 as general health and best vital capacity. PC3 accounted for 19.0% of the variance in the data set, with an eigenvalue of 1.14, and represents the positive correlation between

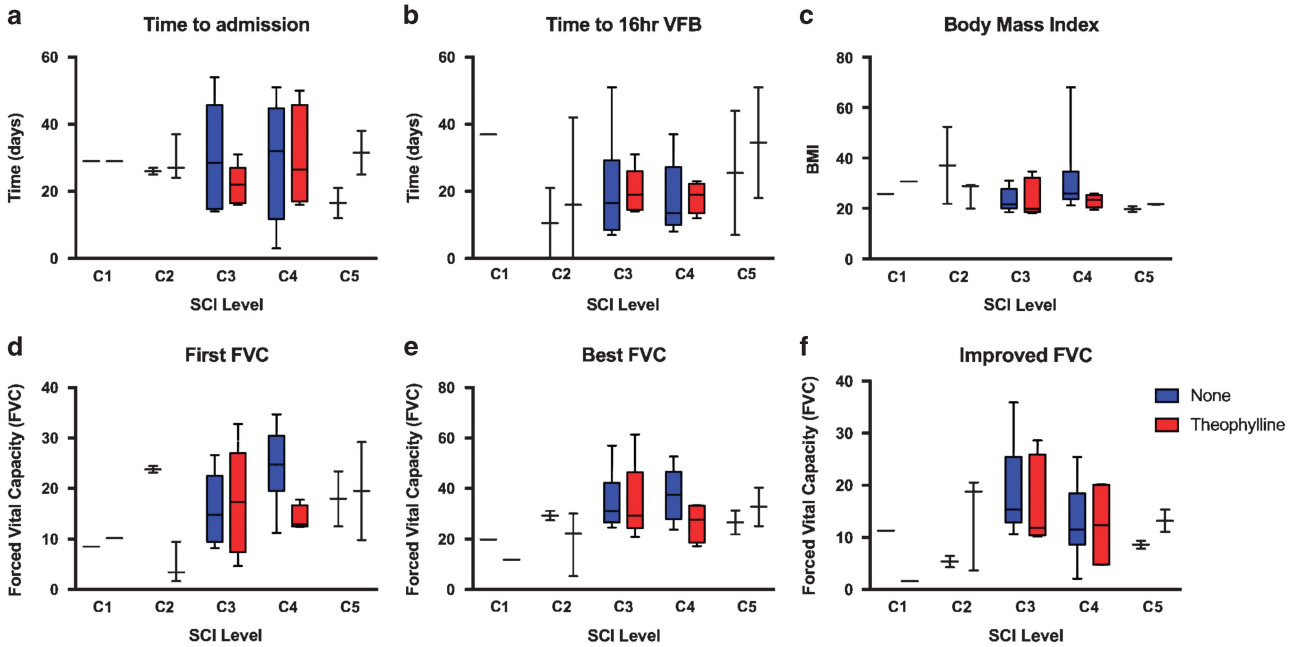


Figure 3 Univariate effects of theophylline treatment on clinically relevant variables of respiratory function. Box and whisker plots illustrating the full range (boxes) and median values for measures of respiratory function, grouped to test the interaction between SCI level (C1–C5) and theophylline treatment for (**a**) time to admission after SCI, time to 16 h of (**b**) VFB, (**c**) BMI, (**d**) first FVC, (**e**) best FVC and (**f**) improved FVC. No significant interactions between SCI level and treatment condition were found for any of the measures individually.

BMI and time from injury to admission (Figure 2a, bottom panel, original, PC3), which remained stable after bootstrapping (Figure 2a, bottom panel, bootstrapped, PC3). Based on this, we have named PC3 as health and latency to hospital. General linear model hypothesis tests on the full outcome space described by the PC1–PC3 score axes revealed a significant multidimensional interaction between theophylline treatment and SCI level (Wilks' Lambda, $F(12,64)=2.115$, $P=0.028$, $\eta^2=0.256$, $1-\beta=0.837$; Figure 2b, top panel, original), which remained stable after bootstrapping (Wilks' Lambda, $F(12,64)=2.381$, $P=0.013$, $\eta^2=0.278$, $1-\beta=0.886$; Figure 2b, bottom panel, bootstrapped). *Post hoc* testing on each PC on its own (Figure 2c) found a significant interaction between theophylline treatment and SCI level on PC1 ($F(4,26)=3.828$, $P=0.014$, $\eta^2=0.371$, $1-\beta=0.830$; Figure 2c, top panel, original), which remained stable after bootstrapping ($F(4,26)=3.631$, $P=0.018$, $\eta^2=0.358$, $1-\beta=0.807$; Figure 2c top panel, bootstrapped). The effect of theophylline on PC2 and PC3 did not reach significance (both $F(4,26)<1.90$, $P>0.05$, $\eta^2<0.25$, $1-\beta<0.55$; Figure 2c, middle and bottom panel, original and bootstrapped). Effect sizes were calculated from the hypotheses tests of the interaction between treatment and SCI level on the PC scores generated using the NL-PCA. Significant effect sizes were only able to be detected when calculated from the PC scores and not the individual univariate outcomes.

The interpretation of this analysis is that the use of theophylline explained 25.6% of the variability within the model with a low likelihood of type 1 error ($<$ 2.8%) and a high statistical power of 83.7%. The top left panel in Figure 2c (label PC1 score) shows a large effect size of theophylline (red bars), which trends from strongly negative to weakly positive across the PC1 space. The high degree of variability in the NL-PCA may suggest that there are responders and nonresponders, which make treatment effects difficult to detect at the univariate level (Figure 3).

Univariate analysis of health and respiratory function

Univariate hypothesis testing of individual outcomes, including time to admit, time to achieve 16 h of VFB, BMI, first FVC, best FVC and improvement in FVC is presented in Figure 3, based on the interaction between theophylline treatment and SCI level. Rates of successful ventilator weaning by risk factor are presented in Table 3 (values presented are *P*-values derived from Pearson chi-square). Success in ventilator liberation was strongly correlated with level of injury for 16 h of VFB ($P=0.0082$) and 24 h of VFB ($P=0.0003$). Likewise, first FVC was strongly correlated with achievement of 24 h of ventilator-free breathing ($P=0.0110$). Gender and age were moderately associated with weaning success with $P=0.0309$ for 16 h of VFB and $P=0.0383$ for 24 h of VFB. Achievement of 24 h of VFB approached significance for mechanism of injury ($P=0.0700$), absence of pleural effusion ($P=0.0878$), absence of unilateral hemidiaphragm elevation ($P=0.1314$). In this study, the rates of successful VFB were not significantly correlated with impairment scale (limited to AIS A or B at enrollment), bronchoscopy before admission, asthma, smoking, obstructive sleep apnea, chronic obstructive pulmonary disease, history of pneumothorax or BMI.

Fourteen patients were treated with oral theophylline at a dose of 200–300 mg per day split into twice or three times daily dosing for 7 or more days (mean 22 days, median 20 days). Among those treated for greater than 7 days, theophylline was discontinued in six cases due to adverse events including loose stool ($N=2$), increased anxiety ($N=2$), acute interstitial nephritis ($N=1$; not confirmed to be related to theophylline) and concern of increased risk of arrhythmia in one patient with pre-existing cardiac disease. These cases were all statistically analyzed as having been treated with theophylline.

Our univariate analysis of theophylline's impact on ventilator weaning rates was underpowered to determine effect and did not reach statistical significance. Further analysis suggested that the use of oral theophylline could be a factor in our relatively high ventilator

Table 3 Predictors of ventilator-free breathing

Risk factor	*16 h VFB (P-value)*	*24 h VFB (P-value)*
Gender	0.0309	0.3464
Age	0.3470	0.0383
Mechanism of injury	0.1170	0.0700
Level of injury	0.0082	0.0003
Impairment Scale	0.4185	0.8415
Bronchoscopy before admission	0.5465	0.3711
Asthma	0.6608	0.5152
Smoking	0.7598	0.6502
OSA	0.5854	0.4185
COPD	0.6608	0.5152
Pneumothorax	1.0000	1.0000
Hemi-diaphragm	0.3091	0.1314
Pleural effusion	0.2498	0.0878

Abbreviations: COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; VFB, ventilator-free breathing.

weaning rates. Only when assessed in a multivariate space, combined with stability testing for potential outlier influences, are any potential treatment effects detected. Importantly, we also found oral theophylline to be safe at the low doses described above.

DISCUSSION

This descriptive study provides the first known data on achievable rates of partial and complete ventilator weaning after motor-complete high cervical SCI. We propose that daytime ventilator independence (16 h of VFB) is a clinically important and attainable goal for high cervical SCI patients who might otherwise fail to be completely liberated from mechanical ventilation. Indeed, there are both SCI and non-SCI-related reasons why a person may have difficulty weaning off the ventilator at night. We found that our cohort demographics are consistent with national trends in age, gender and mechanism of injury. Our analysis revealed that 100% of patients with C3–C5 and 50–60% of C1–C2 SCI were able to achieve daytime ventilator independence. For those with SCI, weaning from mechanical ventilation is likely to facilitate improved social participation and decreased costs and caregiver burden.[24,25]

The findings presented here also offer an important update to expected rates of complete (24 h of VFB) ventilator weaning. Table 4 presents our results in comparison with previously published rates of successful ventilator weaning, defined as 24 h of VFB.[3,26] The reasons for our improved rates of ventilator weaning are likely multiple including increased implementation of noninvasive ventilation strategies, positive pressure treatments and consistent use of mechanical insufflation–exsufflation in the multidisciplinary respiratory care of these patients at our center, and possibly the use of theophylline.

Our study has multiple limitations inherent in the fact that this is a retrospective analysis with a small sample size. As a retrospective study, there was inherent bias in the selection of patients who received theophylline compared with those who did not. There was a change in practice at our center in December 2013 after which theophylline was routinely administered to patients with high cervical injuries. Patients who received theophylline had increased rates of smoking, decreased FVC on admission and were generally those with less preservation of diaphragmatic innervation based on the level of injury and zone of partial preservation.

Table 4 Comparison of successful ventilator weaning rates reported in literature

Study	*Successful ventilator weaning for given level of SCI (% weaned with AIS A or B)*				
	C1	*C2*	*C3*	*C4*	*C5*
Chiodo *et al.*[26]	NR	0	25	77	50
Wong *et al.*[3]	0	0	75	91	NR
Current data (Table 2)	0	40	91	100	100

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; NR, not reported; SCI, spinal cord injury.

Because of our low numbers, our univariate analysis may have been underpowered to demonstrate significance between ventilator weaning and impairment scale, bronchoscopy before admission, asthma, smoking, obstructive sleep apnea, chronic obstructive pulmonary disease, history of pneumothorax or BMI. We sought to overcome this limitation using principal component analysis and bootstrapping.

NL-PCA is a form of unsupervised machine learning in which the goal is to extract as much variance in a data set with the fewest components. Using a PCA revealed potentially clinically relevant patterns of neurological plasticity in the respiratory function of acute cervical SCI patients treated with theophylline. The present results suggest that advanced analytics can help overcome the limited power of univariate testing performed in prior studies. However, their deployment in low N cohorts risks 'overfitting', potentially limiting the external validity of the findings. Our bootstrapping approach partially mitigates this risk by simulating a larger cohort, lending preliminary support for the idea that theophylline may improve ventilator weaning.

CONCLUSIONS

This study demonstrates a higher rate of successful ventilator weaning in cervical SCI than that previously described, using a regimen of high volume ventilation, medication optimization, noninvasive ventilation and aggressive pulmonary toilet (positive pressure treatments and mechanical insufflation–exsufflation) at our center. Age, gender, level of injury and initial FVC were each found to be significantly associated with achieving VFB. Our initial univariate analysis was underpowered to identify statistically meaningful effects of treatments. However, based on advanced analytics, we suspect that some of our patients' success in ventilator weaning may be attributable to theophylline administration, and that theophylline may have a SCI level-dependent effect on successful ventilator liberation.

The impact of different interventions to improve respiratory function after traumatic SCI remains poorly understood. Even highly anticipated clinical trials such as the recently published use of high vs standard tidal volumes for ventilator weaning have been unable to demonstrate efficacy because of limited sample size.[27] To overcome sample size limitations typical of spinal cord injury clinical trials, we propose that a large multi-center prospective study is needed to fully evaluate a uniform ventilator weaning protocol with or without the use of adjunctive agents such as oral theophylline.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported in part by funding from DoD/CDMRP SCIRP Translational Partnership Award Number: W81XWH-13-1-0297, NIH/NINDS R01NS067092 and Wings for Life Foundation.

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REDcap Database variables summary from over 20,000 currently being collected.

SPINAL CORD INJURY REDCAP DATABASE

Redcap Data Dictionary

Total Variables Collected

As of 10/05/2015: 1,294 Variables

NINDS Common Data Element (CDE) Count

Core-CDE: 199 Variables
Supplementary-CDE: 642 Variables
Exploratory-CDE: 43 Variables

Patient Demographics

General Demographics

Study ID
Medical Record Number
(S-CDE) Facility Name
Patient Last Name
Patient First Name
Year of Injury
(S-CDE) Patient Age at Time of Injury
(C-CDE) Birth Date
(C-CDE) Patient Gender
(C-CDE) Date of Injury
(C-CDE) Time of Injury
Time of Injury Above is
Admitted Service
Primary Insurance Code
Primary Insurance Name
Secondary Insurance Code
Secondary Insurance Name
(C-CDE) Race
(C-CDE) Ethnicity
Language Spoken
(C-CDE) Number of Years of Education
(S-CDE) Marital/Partner Status
(S-CDE) Number of Members in Patient's Household (Including Patient)
(S-CDE) Area of Residence
(S-CDE) Primary Occupation
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) If indicated Paid Work for previous question, please specify.
(S-CDE) Secondary Occupation
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) If indicated Paid Work for previous question, please specify.
(S-CDE) Family Income Range
(E-CDE) How do you get along with your current household income?

(S-CDE) Birth Country Name
(E-CDE) Citizen of USA

Deceased Status

(S-CDE) Patient is Deceased?

Patient Deceased While At Hospital

(S-CDE) Date of Death

(S-CDE) Time of Death

(S-CDE) Primary Cause of Death

(S-CDE) Secondary Cause(s) of Death

Consent and Contact Information

Study Consent

Initial Consent Status

Initial Consent Date
If patient initially enrolled and given blood draw under "Waiver of Consent", Surrogate has signed off to enroll the patient.

Surrogate Full Name

Surrogate Home Phone Number

Surrogate Cell/Alternate Phone Number

Surrogate Address

Surrogate Email Address

Surrogate Relationship to Patient

Subject Reconsent (for patients initially enrolled via waiver or surrogate consent)

Patient Contact Information

Patient Address

Patient Email

Patient Home Phone Number

Patient Cell/Alternate Phone Number

Name of Primary Contact

Phone Number of Primary Contact

Primary Contact's Relationship with Patient

Other Spinal Cord Injury Studies

Enrolled in Other SCI Studies/Trials?

Biospecimens Collection

24 Hour Blood Draw

24 Hour Blood - Was Blood Drawn?

24 Hour Blood - Draw Time

24 Hour Blood - Processing Time

24 Hour Blood - Freezer Time

24 Hour Blood - Notes

48 Hour Blood Draw

48 Hour Blood - Was Blood Drawn?

48 Hour Blood - Draw Time

48 Hour Blood - Processing Time

48 Hour Blood - Freezer Time

48 Hour Blood - Notes

Medical History

Prior Medical History

(S-CDE) Date Medical History Taken
(S-CDE) Does the participant have a history of any medical problems/conditions in the following body systems?
(C-CDE) Please describe allergic/immunologic history indicated above. Include start/end date.
(S-CDE) Is allergic/immunologic condition described above ongoing?
(C-CDE) Please describe cardiovascular history indicated above. Include start/end date.
(S-CDE) Is cardiovascular condition described above ongoing?
(C-CDE) Please describe constitutional symptoms indicated above. Include start/end date.
(S-CDE) Is constitutional symptoms condition described above ongoing?
(C-CDE) Please describe ears/nose/mouth/throat history indicated above. Include start/end date.
(S-CDE) Is ears/nose/mouth/throat condition described above ongoing?
(C-CDE) Please describe endocrine history indicated above. Include start/end date.
(S-CDE) Is endocrine condition described above ongoing?
(C-CDE) Please describe eye history indicated above. Include start/end date.
(S-CDE) Is eye condition described above ongoing?
(C-CDE) Please describe gastrointestinal history indicated above. Include start/end date.
(S-CDE) Is gastrointestinal condition described above ongoing?
(C-CDE) Please describe genitourinary history indicated above. Include start/end date.
(S-CDE) Is genitourinary condition described above ongoing?
(C-CDE) Please describe hematogenic/lymphatic history indicated above. Include start/end date.
(S-CDE) Is hematogenic/lymphatic condition described above ongoing?
(C-CDE) Please describe integumentary (skin and/or breast) history indicated above. Include start/end date.
(S-CDE) Is integumentary condition described above ongoing?
(C-CDE) Please describe musculoskeletal history indicated above. Include start/end date.
(S-CDE) Is musculoskeletal condition described above ongoing?
(C-CDE) Please describe neurological history indicated above. Include start/end date.
(S-CDE) Is neurological condition described above ongoing?
(C-CDE) Please describe psychiatric history indicated above. Include start/end date.
(S-CDE) Is psychiatric condition described above ongoing?
(C-CDE) Please describe respiratory history indicated above. Include start/end date.
(S-CDE) Is respiratory condition described above ongoing?
(C-CDE) Please describe "Other" history indicated above. Include start/end date.
(S-CDE) Is the "Other" condition described above ongoing?
(E-CDE) Types of cardiovascular conditions present before spinal cord lesion
(E-CDE) Cardiac pacemaker: date last inserted
(E-CDE) Please specify other cardiac disorders.
(E-CDE) Cardiac surgery: specify type of surgery or mechanical intervention the participant/patient underwent
(E-CDE) Cardiac surgery: date last performed
(E-CDE) Please specify Other selected above regarding cardiovascular history

(E-CDE) Pulmonary conditions present before the spinal cord lesion
(E-CDE) Please specify Other selected above regarding pulmonary history
(E-CDE) Endocrine & Metabolic conditions diagnosed before the spinal cord lesion
(E-CDE) Diabetes mellitus type
(E-CDE) Please specify lipid disorder
(E-CDE) Method used to diagnosis osteoporosis
(E-CDE) Please specify thyroid disease diagnosis
(E-CDE) Please specify Other selected above regarding endocrine and metabolic history
(E-CDE) Neuro-Musculoskeletal history before the spinal cord lesion
(E-CDE) Specifies name of pre-existing congenital deformity of the spine and spinal cord
(E-CDE) Anatomic site of pre-existing congenital deformity of spine and spinal cord
(E-CDE) Previous surgery due to congenital deformities of spine and spinal cord
(E-CDE) Date of surgery for congenital deformity
(E-CDE) Description of surgery caused by pre-existing congenital deformities of spine and spinal cord
(E-CDE) Specify name of pre-existing systemic neuro-degenerative disorder
(E-CDE) Specify location/anatomic site of pre-existing systemic neurodegenerative disorder
(E-CDE) Previous surgery due to neurodegenerative disorder
(E-CDE) Date of surgery caused by neurodegenerative disorder
(E-CDE) Description of surgery caused by neurodegenerative disorder
(E-CDE) Specify diagnosis of pre-existing degenerative spine disorder
(E-CDE) Specify location/anatomic site of pre-existing degenerative spine disorder
(E-CDE) Surgery due to degenerative spine disorder
(E-CDE) Date of surgery caused by degenerative spine disorder
(E-CDE) Description of surgery caused by degenerative spine disorder
(E-CDE) Urinary Tract Impairment before the spinal cord lesion
(E-CDE) Please specify
(E-CDE) Gastrointestinal or anal sphincter dysfunction before the spinal cord lesion
(E-CDE) Please specify

Prior and Concomitant Medications

(S-CDE) Did the patient take any medications prior to enrollment?
(S-CDE) Medication Name
(S-CDE) Reason For Administration of a Prior/Concomitant Agent or Measure
(S-CDE) Dose
(S-CDE) Frequency
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Route
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Start Date
(S-CDE) End Date
(S-CDE) Ongoing?
(S-CDE) Any Vasopressor Use
(S-CDE) Urinary Tract Drugs Within The Last Year
(S-CDE) If indicated Other for previous question, please specify.

(S-CDE) Medication Affecting Bowel Function/Constipating Agents (Within the Last 4 Weeks):

(S-CDE) If indicated Other for previous question, please specify.

(S-CDE) Medication Affecting Bowel Function- Oral Laxatives (Within the Last 4 Weeks):

(S-CDE) If indicated Other for previous question, please specify.

(S-CDE) Medication Affecting Cardiovascular Function on the Day of Examination

(S-CDE) If indicated Other for previous question, please specify.

(S-CDE) Treatment for Spasticity/Spasms Within the Last 4 Weeks

S-CDE) Does the participant have any other serious co-morbid or concomitant medical condition that, in the opinion of the investigator, would compromise the safety of the patient/participant or compromise the participant's ability to participate in the study?

Alcohol and Tobacco Use

(S-CDE) How often do you have a drink containing alcohol?
(S-CDE) How often do you have five or more drinks on one occasion?
(S-CDE) Tobacco smoking history
(S-CDE) Which year did you quit smoking?
(S-CDE) For how many years did (have) you smoked
(S-CDE) On average, how many cigarettes do (did) you smoke on a daily basis?
(S-CDE) On average, how many cigars do (did) you smoke on a daily basis?
(S-CDE) On average, how many pipe bowls do (did) you smoke on a daily basis?
(S-CDE) Number of pack-years of smoking

Substance Use

(S-CDE) During the last 12 months (or during the time since your injury - if year 1 follow-up) did you use any illicit or non-prescription drugs?
(S-CDE) If Yes above, please indicate the drugs used
(S-CDE) List other drugs used

Family History

(E-CDE) Family History Medical Condition Types

(E-CDE) If indicated Other for previous question, please specify.

(E-CDE) Relationship of the Family Member or Ancestor with the Medical Condition or Health Related Event to the Participant

Trauma Characteristics

EMS History

(S-CDE) Date and Time first call received by EMS
(S-CDE) Date and Time of EMS dispatch
(S-CDE) EMS dispatch priority
(S-CDE) Type of EMS vehicle
(S-CDE) Date and Time of EMS arrival at scene
(S-CDE) Date and Time of EMS departure from scene
(S-CDE) Highest level of EMS service
Pre-Hospital Transport Time (Dispatch to Arrival)
(S-CDE) Date and time of EMS GCS
(S-CDE) GCS From EMS Report
(S-CDE) Best GCS Eye Response Score
(S-CDE) Best GCS Verbal Response Score
(S-CDE) Best GCS Motor Response Score
(S-CDE) AIS 6 Body Regions: Head & Neck
(S-CDE) AIS 6 Body Regions: Face
(S-CDE) AIS 6 Body Regions: Chest
(S-CDE) AIS 6 Body Regions: Abdomen
(S-CDE) AIS 6 Body Regions: Extremity
(S-CDE) AIS 6 Body Regions: External

(S-CDE) AIS 9 Body Regions: Head
(S-CDE) AIS 9 Body Regions: Neck
(S-CDE) AIS 9 Body Regions: Face
(S-CDE) AIS 9 Body Regions: Chest/Thorax
(S-CDE) AIS 9 Body Regions: Abdomen
(S-CDE) AIS 9 Body Regions: Spine
(S-CDE) AIS 9 Body Regions: Upper Extremity
(S-CDE) AIS 9 Body Regions: Lower Extremity
(S-CDE) AIS 9 Body Regions: External and Other

ED History

(S-CDE) ED Time of Arrival
(C-CDE) ED Date of Arrival
Transport Blood Pressure
Transport Heart Rate
(S-CDE) ISS Score on Arrival
(S-CDE) Intubated on Arrival
Total Time in ER
Time to OR
ED/EMS Description of Trauma
(C-CDE) ED ASIA Impairment Scale (AIS)
(C-CDE) ED Neurological Level of Injury
ASIA Grade from PMR
(C-CDE) Spinal Cord Injury Etiology
Spinal Cord Injury Etiology Description
(S-CDE) Iatrogenic Role in the Etiology
(S-CDE) Timeframe of onset of NTSCI (non-traumatic spinal cord injury)
(S-CDE) Classification of etiology of Non- Traumatic Spinal Cord Injury (NTSCI)- Axis 1- Level 1
(S-CDE) Classification of etiology of Non- Traumatic Spinal Cord Injury (NTSCI)- Axis 1- Level 2
(S-CDE) Classification of etiology of Non- Traumatic Spinal Cord Injury (NTSCI)- Axis 1- Level 3
(S-CDE) Classification of etiology of Non- Traumatic Spinal Cord Injury (NTSCI)- Axis 1- Level 4
(S-CDE) Classification of etiology of Non- Traumatic Spinal Cord Injury (NTSCI)- Axis 1- Level 5
Working Diagnosis
(S-CDE) Level of Care (provided to participant by health care facility)
(S-CDE) ED GCS Score
(C-CDE) Best GCS Eye Response Score
(C-CDE) Best GCS Verbal Response Score
(S-CDE) Best GCS Motor Response Score
TBI Present?
TBI Diagnosis
Loss of Consciousness
(S-CDE) Associated Injury (Includes moderate to severe traumatic brain injury[GCS< 12], non-vertebral fractures requiring surgery, severe facial injuries affecting sense organs, major chest injury requiring chest-tube or mechanical ventilation, traumatic amputations of an arm or leg (or injuries severe enough to require surgical amputation), severe hemorrhaging, or damage to any internal organ requiring surgery)
Extremity Fractures
(S-CDE) Penetrating/Blunt Injury

Hemorrhagic Injury

Central Cord Injury

Cervical Injury

Vertebral Fracture

(S-CDE) Spinal Column Injury/ies (any disruption through the spinal column including the bony vertebral elements and their supporting ligaments, capsules, discs, and other supporting soft tissues)

(S-CDE) Single or Multiple Spinal Column Level Injury/ies

(S-CDE) Spinal Column Injury Level

(S-CDE) Disc/Posterior Ligamentous Complex Injury

(S-CDE) Traumatic Translation

Peripheral Abrasions?

Vertebral Artery Injury

T2 Weighted Image

History of Hypertension

Patient History of Anti-coagulation Therapy

Type of Anti-coagulation/Anti-Platelet Therapy

Past History of TBI

Past History of SCI

(S-CDE) On Paralytics Pre-hospital Arrival

(S-CDE) Sedated Pre-hospital Arrival

(S-CDE) Hypotensive Episode Pre-hospital Arrival

(S-CDE) Hypoxic Episode Pre-hospital Arrival

ED Rectal Tone

Neurological Exam

(CDE CORE) Date of Neurological Examination
(C-CDE) Sensory Level - Left
(C-CDE) Sensory Level - Right
(C-CDE) Motor Level - Left
(C-CDE) Motor Level – Right

ED Vitals

(S-CDE) Date Vitals Performed
(S-CDE) Time Examination Performed
(S-CDE) Height
(S-CDE) Weight
(S-CDE) Position During Blood Pressure Testing
(S-CDE) Compression Devices in Use During Testing
(S-CDE) Pulse
(S-CDE) Pulse Findings
(S-CDE) Blood Pressure - Systole
(S-CDE) Blood Pressure - Diastole
(S-CDE) Mean Arterial Pressure Measurement
(S-CDE) Temperature
(S-CDE) Method Temperature Measured
(S-CDE) Forced Vital Capacity (FVC)
(S-CDE) Forced Expiratory Volume in One Second (FEV1)
(S-CDE) Peak Expiratory Flow (PEF)
(S-CDE) Oxygen Saturation %
(S-CDE) Was a fasting lipid profile conducted while the patient was on anti-lipid therapy?
(E-CDE) Triglycerides (TG)

(E-CDE) LDL Cholesterol
(E-CDE) HDL Cholesterol
(E-CDE) Total Cholesterol (TC)

Blood Pressure Management

Hospital Blood Pressure Management

ICU MAP Goals
ICU Missed Map Goals
# of PRBC Units Transfused
# of Units of Blood Transfused
First Vasopressor Used
Max Dosage of Vasopressor 1
Was the Pressor Changed?
Second Vasopressor Used
Max Dosage of Vasopressor 2
2nd Vasopressor Added to the First?
Please Describe the Vasopressors Added Together
Two or More Vasopressors Used?
Dopamine Complications
Neo Complications
(S-CDE) ED Hypotension (Systolic < 100)
(S-CDE) ED Hypotension (Systolic < 90)
(S-CDE) ED Hypotension (Systolic < 80)
(S-CDE) ED Hypotension (Systolic < 70)
ED Bradycardia
ED Fluid Bolus
ED Vasopessor Given
(S-CDE) OR Hypotension (Systolic < 100)
(S-CDE) OR Hypotension (Systolic < 90)
Upload ICU MAP

Operating Room

SCI OR Procedures

Date of Last Surgical Intervention
SCI Surgical Procedure 1 Name
SCI Surgical Procedure 1 CPT
SCI Surgical Procedure 2 Name
SCI Surgical Procedure 2 CPT
SCI Surgical Procedure 3 Name
SCI Surgical Procedure 3 CPT
Age At Time of Surgery
Surgery Date
Patient Weight
Format of the operation room in the Anesthesia Report for the subject's operation
Format A: Time in which anesthesia care is started

Format A: Time in which anesthesia care ends
Format A: Time induction is started on the patient
Format A: Time in which induction ends
Format A: Procedure start time on patient
Format A: Procedure end time on patient
Format A: Time that all OR tasks end
Format B: Anesthesia care start time
Format B: Anesthesia end time
Format B: Time in which anesthesia starts in the OR
Format B: Time in which anesthesia leaves the OR
Format B: Time in which anesthesia ends in the OR
Format A & B: Time in which first incision was made
Closure Time
Total time from procedure start to procedure end (minutes)
Type of surgery patient underwent. Types include Spinal Cord Injury [SCI]: Laminectomy and Non-SCI.
Polytrauma noted in OR report
Method used for intubation
ABG lab value for partial pressure of oxygen - Reading 1
ABG lab value for partial pressure of oxygen - Reading 2
ABG lab value for partial pressure of oxygen - Reading 3
ABG lab value for partial pressure of oxygen - Reading 4
ABG lab value for partial pressure of oxygen - Reading 5
ABG lab value for partial pressure of oxygen - Reading 6
ABG lab value for partial pressure of oxygen - Reading 7
ABG lab value for partial pressure of oxygen - Reading 8
ABG lab value for partial pressure of oxygen - Reading 9
ABG lab value for partial pressure of oxygen - Reading 10
Anesthesia
Whether a steroid was used in the operation
Steroid Type
Pre-operative Hematocrit
Type of vasopressor used during the surgery
Patient received Phenylephrine as a vasopressor during the operation (Includes Neosynephrine)
Patient received Dopamine as a vasopressor during the operation
Patient received Norepinephrine as a vasopressor during the operation (Includes Levophed)
Type of anesthesia used during surgery
Packed red blood cell's [PRBC] given to patient during surgery
Crystalloids given to patient during surgery
Lab value of hematocrit obtained at some point during surgery
Upload OR Time Specific Data
Additional OR information regarding the patient

Interventions

Hospital Interventions

(S-CDE) Admitted to Special Care Unit at Any Time During Their Stay (Includes ICU and Step-Down Units)
(S-CDE) Type of Special Care Unit
(S-CDE) Special Care Unit Admission Date
Special Care Unit Admission Time
History of Present Illness
Bolt (ICP) Placement
EVD Placement
Lumbar Drain Placement
Spinal Surgery
Other Surgical Interventions
Methylprednisolone/Steroid Treatment?
Please specify Other indicated above
(S-CDE) Date(s) Steroid Administered
Neuro-Monitoring?
Neuro-Monitoring Alarm During Procedure?
Neuro-Monitoring Notes
Anesthesia
OR MAP
Current levels wrist
Current level ankle
Baseline LN20
Baseline RN20
Baseline LP45
Baseline RP45
Baseline Volts Lupper
Baseline Volts Rupper
Baseline Volts Llower
Baseline Volts Rlower
End SSEP LN20
End SSEP RN20
End SSEP Lp45
End SSEP Rp45
End Volts Lupper
End Volts Rupper
End Volts Llower
End Volts Rlower
Signal Quality
SSEP compared to exam
MEP compared to exam
Restraints Utilized/Required
Intubation
Reintubation
Ventilatory Assistance Utilized
Please specify Other indicated above
Number of Days on Ventilator
Tracheostomy
Gastrostomy/PEG
Central Venous Cath
Peripheral Inserted Central Cath (PICC)
Arterial Line
Renal Replacement Therapy
Reversal of Coagulopathy on Admission?
ECG Notes

Muscle and Sensory Exams

Neurosurgery Service Consult

Neurosurgery Service Consult
Neurosurgery Consult Date
Neurosurgery Consult Time
Left Bicep Strength
Left Deltoid Strength
Left EHL Strength
Left Gastro Strength
Left Grip Strength
Left Hamstring Strength
Left Interos Strength
Left IP Strength
Left Quad Strength
Left TA Strength
Left Tricep Strength
Left WE Strength
Left WF Strength
Right Bicep Strength
Right Deltoid Strength
Right EHL Strength
Right Gastro Strength
Right Grip Strength
Right Hamstring Strength
Right Interos Strength
Right IP Strength
Right Quad Strength
Right TA Strength
Right Tricep Strength
Right WE Strength
Right WF Strength

ISNCSCI Exam

Was ISNCSCI Completed?
(C-CDE) Date of Exam
(C-CDE) Time of Exam
(C-CDE) Neurological Level of Injury
(C-CDE) Complete or Incomplete?
(C-CDE) ASIA Impairment Scale
(C-CDE) Sensory Neurological Level - Right
(C-CDE) Sensory Neurological Level - Left
(C-CDE) Motor Neurological Level - Right
(C-CDE) Motor Neurological Level - Left
(C-CDE) Motor Upper Limb Subtotal - Right
(C-CDE) Motor Upper Limb Subtotal - Left
(C-CDE) Motor Upper Limb Total - Right + Left
(C-CDE) Motor Lower Limb Subtotal - Right
(C-CDE) Motor Lower Limb Subtotal - Left
(C-CDE) Motor Lower Limb Total - Right + Left
(C-CDE) Sensory Light Touch Subtotal - Right
(C-CDE) Sensory Light Touch Subtotal - Left
(C-CDE) Sensory Light Touch Total - Right + Left
(C-CDE) Sensory Pin Prick Subtotal - Right
(C-CDE) Sensory Pin Prick Subtotal - Left
(C-CDE) Sensory Pin Prick Total - Right + Left
(C-CDE) Voluntary Anal Contraction (VAC)

(C-CDE) Any Anal Sensation
(C-CDE) Zone of Partial Preservation: Motor Right
(C-CDE) Zone of Partial Preservation: Motor Left
(C-CDE) Zone of Partial Preservation: Sensory Right
(C-CDE) Zone of Partial Preservation: Sensory Left
(C-CDE) Motor Elbow Flexors - Right
(C-CDE) Motor Wrist Extensors - Right
(C-CDE) Motor Elbow Extensors - Right
(C-CDE) Motor Finger Flexors - Right
(C-CDE) Motor Finger Abductors - Right
(C-CDE) Motor Hip Flexors - Right
(C-CDE) Motor Knee Extensors - Right
(C-CDE) Motor Ankle Dorsiflexors - Right
(C-CDE) Motor Long Toe Extensors - Right
(C-CDE) Motor Ankle Plantar Flexors - Right
(C-CDE) Motor Elbow Flexors - Left
(C-CDE) Motor Wrist Extensors - Left
(C-CDE) Motor Elbow Extensors - Left
(C-CDE) Motor Finger Flexors - Left
(C-CDE) Motor Finger Abductors - Left
(C-CDE) Motor Hip Flexors - Left
(C-CDE) Motor Knee Extensors - Left
(C-CDE) Motor Ankle Dorsiflexors - Left
(C-CDE) Motor Long Toe Extensors - Left
(C-CDE) Motor Ankle Plantar Flexors - Right
(C-CDE) Sensory Light Touch C2 - Right
(C-CDE) Sensory Light Touch C3 - Right
(C-CDE) Sensory Light Touch C4 - Right
(C-CDE) Sensory Light Touch C5 - Right
(C-CDE) Sensory Light Touch C6 - Right
(C-CDE) Sensory Light Touch C7 - Right
(C-CDE) Sensory Light Touch C8 - Right
(C-CDE) Sensory Light Touch T1 - Right
(C-CDE) Sensory Light Touch T2 - Right
(C-CDE) Sensory Light Touch T3 - Right
(C-CDE) Sensory Light Touch T4 - Right
(C-CDE) Sensory Light Touch T5 - Right
(C-CDE) Sensory Light Touch T6 - Right
(C-CDE) Sensory Light Touch T7 - Right
(C-CDE) Sensory Light Touch T8 - Right
(C-CDE) Sensory Light Touch T9 - Right
(C-CDE) Sensory Light Touch T10 - Right
(C-CDE) Sensory Light Touch T11 - Right
(C-CDE) Sensory Light Touch T12 - Right
(C-CDE) Sensory Light Touch L1 - Right
(C-CDE) Sensory Light Touch L2 - Right
(C-CDE) Sensory Light Touch L3 - Right
(C-CDE) Sensory Light Touch L4 - Right
(C-CDE) Sensory Light Touch L5 - Right
(C-CDE) Sensory Light Touch S1 - Right
(C-CDE) Sensory Light Touch S2 - Right
(C-CDE) Sensory Light Touch S3 - Right
(C-CDE) Sensory Light Touch S4-5 - Right
(C-CDE) Sensory Pin Prick C2 - Right
(C-CDE) Sensory Pin Prick C3 - Right

(C-CDE) Sensory Pin Prick C4 - Right
(C-CDE) Sensory Pin Prick C5 - Right
(C-CDE) Sensory Pin Prick C6 - Right
(C-CDE) Sensory Pin Prick C7 - Right
(C-CDE) Sensory Pin Prick C8 - Right
(C-CDE) Sensory Pin Prick T1 - Right
(C-CDE) Sensory Pin Prick T2 - Right
(C-CDE) Sensory Pin Prick T3 - Right
(C-CDE) Sensory Pin Prick T4 - Right
(C-CDE) Sensory Pin Prick T5 - Right
(C-CDE) Sensory Pin Prick T6 - Right
(C-CDE) Sensory Pin Prick T7 - Right
(C-CDE) Sensory Pin Prick T8 - Right
(C-CDE) Sensory Pin Prick T9 - Right
(C-CDE) Sensory Pin Prick T10 - Right
(C-CDE) Sensory Pin Prick T11 - Right
(C-CDE) Sensory Pin Prick T12 - Right
(C-CDE) Sensory Pin Prick L1 - Right
(C-CDE) Sensory Pin Prick L2 - Right
(C-CDE) Sensory Pin Prick L3 - Right
(C-CDE) Sensory Pin Prick L4 - Right
(C-CDE) Sensory Pin Prick L5 - Right
(C-CDE) Sensory Pin Prick S1 - Right
(C-CDE) Sensory Pin Prick S2 - Right
(C-CDE) Sensory Pin Prick S3 - Right
(C-CDE) Sensory Pin Prick S4-5 - Right
(C-CDE) Sensory Light Touch C2 - Left
(C-CDE) Sensory Light Touch C3 - Left
(C-CDE) Sensory Light Touch C4 - Left
(C-CDE) Sensory Light Touch C5 - Left
(C-CDE) Sensory Light Touch C6 - Left
(C-CDE) Sensory Light Touch C7 - Left
(C-CDE) Sensory Light Touch C8 - Left
(C-CDE) Sensory Light Touch T1 - Left
(C-CDE) Sensory Light Touch T2 - Left
(C-CDE) Sensory Light Touch T3 - Left
(C-CDE) Sensory Light Touch T4 - Left
(C-CDE) Sensory Light Touch T5 - Left
(C-CDE) Sensory Light Touch T6 - Left
(C-CDE) Sensory Light Touch T7 - Left
(C-CDE) Sensory Light Touch T8 - Left
(C-CDE) Sensory Light Touch T9 - Left
(C-CDE) Sensory Light Touch T10 - Left
(C-CDE) Sensory Light Touch T11 - Left
(C-CDE) Sensory Light Touch T12 - Left
(C-CDE) Sensory Light Touch L1 - Left
(C-CDE) Sensory Light Touch L2 - Left
(C-CDE) Sensory Light Touch L3 - Left
(C-CDE) Sensory Light Touch L4 - Left
(C-CDE) Sensory Light Touch L5 - Left
(C-CDE) Sensory Light Touch S1 - Left
(C-CDE) Sensory Light Touch S2 - Left
(C-CDE) Sensory Light Touch S3 - Left
(C-CDE) Sensory Light Touch S4-5 - Left
(C-CDE) Sensory Pin Prick C2 - Left

(C-CDE) Sensory Pin Prick C3 - Left
(C-CDE) Sensory Pin Prick C4 - Left
(C-CDE) Sensory Pin Prick C5 - Left
(C-CDE) Sensory Pin Prick C6 - Left
(C-CDE) Sensory Pin Prick C7 - Left
(C-CDE) Sensory Pin Prick C8 - Left
(C-CDE) Sensory Pin Prick T1 - Left
(C-CDE) Sensory Pin Prick T2 - Left
(C-CDE) Sensory Pin Prick T3 - Left
(C-CDE) Sensory Pin Prick T4 - Left
(C-CDE) Sensory Pin Prick T5 - Left
(C-CDE) Sensory Pin Prick T6 - Left
(C-CDE) Sensory Pin Prick T7 - Left
(C-CDE) Sensory Pin Prick T8 - Left
(C-CDE) Sensory Pin Prick T9 - Left
(C-CDE) Sensory Pin Prick T10 - Left
(C-CDE) Sensory Pin Prick T11 - Left
(C-CDE) Sensory Pin Prick T12 - Left
(C-CDE) Sensory Pin Prick L1 - Left
(C-CDE) Sensory Pin Prick L2 - Left
(C-CDE) Sensory Pin Prick L3 - Left
(C-CDE) Sensory Pin Prick L4 - Left
(C-CDE) Sensory Pin Prick L5 - Left
(C-CDE) Sensory Pin Prick S1 - Left
(C-CDE) Sensory Pin Prick S2 - Left
(C-CDE) Sensory Pin Prick S3 - Left
(C-CDE) Sensory Pin Prick S4-5 – Left

Hospital Outcomes

Patient Hospital Outcomes

(S-CDE) Discharge Location Type
Discharge Location
(C-CDE) Facility Discharge Date
(S-CDE) Facility Discharge Time
ICU Care
ICU Length of Stay
(C-CDE) Hospital Length of Stay
(S-CDE) Vital Status on Discharge
(C-CDE) ASIA Grade on Discharge
Degree Of ASIA Improvement
(S-CDE) Utilization of Ventilator Assistance on Discharge
Stroke
Alcohol Withdrawal
Pneumonia
Respiratory Failure
UTI
Acute Renal Insufficiency
Central Venous Catheter Infection
Surgical Site Infection
DVT
Pulmonary Embolism
GCS On Discharge
Best GCS Eye Response Score
Best GCS Verbal Response Score
Best GCS Motor Response Score

(C-CDE) Date of Final Inpatient Neurological Exam
(C-CDE) Sensory Level - Left
(C-CDE) Sensory Level - Right
(C-CDE) Motor Level - Left
(C-CDE) Motor Level - Right
Wound Complications
Additional Notes

Imaging

MRI

MRI Imaging?
(S-CDE) MRI Study Date and Time
Hours to MRI
(S-CDE) MR Anatomic Area
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Imaging Scanner Manufacturer Name
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Imaging Scanner Model Name
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Imaging Scanner Strength
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Imaging Scanner Software Version Number
(S-CDE) Image Quality
MRI T2 Axial Available?
Upload T2 Axial File
MRI T2 Sagittal Available?
Upload T2 Sagittal
MRI T2 MERGE Available?
Upload T2 MERGE
MRI T2 Diffusion Available?
Upload T2 Diffusion
MRI Additional Imaging Modality?
MRI MSCC
MRI MCC
Long Extent of T2 Signal
Sag Grade
MRI BASIC Score
Macroscopic Hemorrhage Present?
Epicenter Cord Surface Area (CSA)
Percentage White Matter T2 Hyperintensity
Percentage Grey Matter
(S-CDE) Pre-Existing Hardware/Surgery?
(S-CDE) Type of Pre-Existing Hardware/Surgery
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) If yes, provide an upper limit of instrumentation
(S-CDE) Lower limit
(S-CDE) Exam pulse sequence inventory
(S-CDE) Exam pulse sequence inventory
(S-CDE) Injury type
(S-CDE) Subluxation/translation level
(S-CDE) Measure of subluxation from posterior aspect of vertebral body relative to nearest adjacent body
(S-CDE) Angulation level
(S-CDE) Extra-axial fluid upper limit
(S-CDE) Extra-axial fluid lower limit
(S-CDE) Extra-axial fluid point of maximum compression

(S-CDE) Vertebral fracture upper level
(S-CDE) Vertebral fracture lower level
(S-CDE) Traumatic herniated nucleus polposus (HNP) level
(S-CDE) Traumatic herniated nucleus polposus (HNP) type
(S-CDE) Ligamentous injury/rupture
(S-CDE) Ligamentous injury/rupture
(S-CDE) Ligamentous injury/rupture level
(S-CDE) Degenerative features
(S-CDE) Degenerative features indicator
(S-CDE) Provide the upper limit of abnormality
(S-CDE) Lower limit
(S-CDE) Canal/cord measurements type
(S-CDE) Sagittal canal diameter rostral injury
(S-CDE) Sagittal canal diameter injury
(S-CDE) Sagittal canal diameter caudal to injury
(S-CDE) Cord diameter rostral to injury sagittal
(S-CDE) Spinal cord diameter rostral to injury transverse
(S-CDE) Cord diameter injury sagittal
(S-CDE) Cord diameter injury transverse
(S-CDE) Cord diameter caudal sagittal
(S-CDE) Cord diameter caudal transverse
(S-CDE) Level
(S-CDE) Acute ACI features
(S-CDE) Level [Range4 FM-L3.3]
(S-CDE) Integer range [1-50]
(S-CDE) Cord transection
(S-CDE) Chronic SCI features
(S-CDE) Chronic SCI feature indicator
(S-CDE) Upper level [Range4 FM-L3]
(S-CDE) Lower level [Range4 FM-L3]
(S-CDE) Caliber [Integer range 1-10]
(S-CDE) Length [Integer range 1-60]
Dates of Additional MRIs

CT

CT Available?
(S-CDE) CT Study Date and Time
Number of CT Scans
Dates of CT Scans
CTA Available
Number of CTA Scans
Dates of CTA Scans
DTI Available?

DTI

(S-CDE) DTI Study Date and Time
(S-CDE) Name of Scanner Manufacturer
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Name of scanner software that runs the imaging camera
(S-CDE) Version number of the imaging scanner software
(S-CDE) Magnetic Field Strength of Scanner Used
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Imaging Pulse Sequence Used
(S-CDE) Slide Orientation
(S-CDE) Frame of Reference
(S-CDE) Repetition Time (TR)
(S-CDE) Echo time (TE)

(S-CDE) FA
(S-CDE) Freq FOV mm
(S-CDE) Matrix Size (Axis 1)
(S-CDE) Matrix Size (Axis 2)
(S-CDE) Number of Slices
(S-CDE) Slice Thickness
(S-CDE) Slice Gap
(S-CDE) Voxel Size (Axis 1)
(S-CDE) Voxel Size (Axis 2)
(S-CDE) Voxel Size (Axis 3)
(S-CDE) NEX
(S-CDE) Phase-encode direction
(S-CDE) Was fat signal suppressed in imaging acquisition?
(S-CDE) Band Width
(S-CDE) 2DRF Tilt Angle
(S-CDE) Was flow compensation used in imaging acquisition?
(S-CDE) Echo Train Length
(S-CDE) b-value (first)
(S-CDE) b-value (second)
(S-CDE) b-value (third)
(S-CDE) b-value (fourth)

Other

Imaging Notes

Follow Up Measures

Urodynamics Data Set

Urodynamic Questionnaire Completed?
(S-CDE) Date and Time of Data Collection
(S-CDE) Bladder Sensation During Filling Cystometry
(S-CDE) Detrusor Function
(S-CDE) Bladder Compliance During Filling Cystometry
(S-CDE) Urethral Function During Voiding
(S-CDE) Detrussor Leak Point Pressure During Filling Cystometry
(S-CDE) Maximum Detrusor Pressure Filing Cystometry
(S-CDE) Cystometric Bladder Capacity During Filling Cystometry
(S-CDE) Post Void Residual Volume

Lower Urinary Tract Function Data Set

Lower Urinary Tract Function Questionnaire Completed?
Date and Time of Data Collection
(S-CDE) Urinary tract impairment unrelated to spinal cord lesion
(S-CDE) If indicated Yes above, please specify.
(S-CDE) Awareness of the need to empty the bladder
(S-CDE) If indicated Yes for previous question, please specify
(S-CDE) Main bladder emptying
(S-CDE) Supplementary bladder emptying
(S-CDE) Average number of voluntary bladder emptyings per day during the last week
(S-CDE) Any involuntary urine leakage (incontinence) within the last three months
(S-CDE) Collecting appliances for urinary incontinence
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Any drugs for the urinary tract within the last year
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Surgical procedures on the urinary tract?
(S-CDE) If Yes for previous question, what surgical procedures on the urinary tract have been done?
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Date(s) performed

(S-CDE) Any change in urinary symptoms within the last year
Urinary Tract Infection
Urinary Tract Infection Questionnaire Completed?
(S-CDE) Date and Time of Data Collection
(S-CDE) Length of Time of Sign(s)/Symptoms(s)
(S-CDE) Sign(s)/symptom(s)
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Urine dipstick test for nitrite
(S-CDE) Urine dipstick test for leukocyte esterase
(S-CDE) Urinary culture
(S-CDE) Urine culture sequence number
(S-CDE) Species
(S-CDE) Colony Forming Units (CFU) per mL
(S-CDE) The resistance pattern

Bowel Function Data Set

Bowel Function Questionnaire Completed?
(S-CDE) Date and Time of Data Collection
(S-CDE) Administration Method
(S-CDE) Duration of constipation
(S-CDE) Unsuccessful attempts at defecation within the last three months
(S-CDE) Incomplete rectal emptying after defecation within the last three months
(S-CDE) Abdominal bloating within the last three months
(S-CDE) Abdominal pain/discomfort within the last three months
(S-CDE) Any respiratory discomfort shortness of breath difficulty in taking a deep breath considered to be entirely or partly due to a distended abdomen within the last three months
(S-CDE) Perianal pain during defecation within the last three months
(S-CDE) Frequency of flatus incontinence within the last three months
(S-CDE) Frequency of incontinence to liquid stools within the last three months
(S-CDE) Frequency of incontinence to solid stools within the last three months
(S-CDE) Ability to defer defecation for fifteen minutes or more within the last three months
(S-CDE) Position for bowel care within the last three months
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Degree of independency during bowel management within the last three months
(S-CDE) Bowel care facilitators within the last three months
(S-CDE) If indicated Other for previous question, please specify.
(S-CDE) Events and intervals of defecation (1): Average time from initiation of bowel care to stool comes out within the last three months
(S-CDE) Events and intervals of defecation (2): Average time during bowel movement that stool intermittently or continuously comes out with or without assistance within the last three months
(S-CDE) Events and intervals of defecation (3): Average time spent waiting after last stool passes before ending bowel care within the last three months
(S-CDE) Lifestyle alteration due to anal incontinence within the last three months
(S-CDE) Lifestyle alteration due to constipation within the last three months
(S-CDE) Self reported impact on quality of life due to bowel dysfunction
(S-CDE) Anal tone
(S-CDE) Voluntary contraction of the anal canal

Spinal Intervention and Spinal Procedures Data Set

Spinal Intervention and Spinal Procedures Questionnaire Completed?
(S-CDE) Intervention/procedure date and start time:
(S-CDE) Non-surgical bed rest and external immobilization:
(S-CDE) Spinal intervention - closed manipulation and/or reduction of spinal elements:
(S-CDE) Spinal procedure - approach:
(S-CDE) Date and Time of the Intervention Completion or Surgical Closure:
(S-CDE) Surgical procedure - open reduction:
(S-CDE) Surgical procedure - direct decompression of neural elements:

(S-CDE) Surgical procedure - stabilization and fusion: (one to be filled in for each level of injury, starting with the most cephalic injury)
Stabilization and Fusion - Segment Number
(S-CDE) Surgical procedure – stabilization and fusion: (one to be filled in for each level of injury, starting with the most cephalic injury):
Stabilization and Fusion – Segment Level

Upper Extremity Data Set

SCI Upper Extremity Questionnaire Completed?
(S-CDE) Date and Time of Data Collection
(S-CDE) Laterality
Basic Right Hand - Ability to reach and grasp
Basic Right Hand - Shoulder function classification
Basic Left Hand - Ability to reach and grasp
Basic Left Hand - Shoulder function classification
(S-CDE) Use of assistive devices used to enhance upper extremity function
(S-CDE) Complications to upper extremity function like pain, spasms, contractures, edema, etc
(S-CDE) Upper Extremity/Hand Reconstructive Surgery
(S-CDE) Type of surgery
(S-CDE)Specify "Soft tissue reconstruction: Other" indicated above
(S-CDE)Specify "Other" indicated above
(S-CDE) Specify "Implantable FES" indicated above
(S-CDE) Date of surgery(s)

Cardiovascular Function Data Set

Cardiovascular Function Questionnaire Completed?
Date and Time of Data Collection
(S-CDE) Cardiovascular history before spinal cord lesion
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Events related to cardiovascular function after spinal cord lesion
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Cardiovascular function after spinal cord lesion within the last three months
If indicated Cardiac Conditions for previous question, please specify
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Any medication affecting cardiovascular function on the day of examination
(S-CDE) If indicated Other for previous question, please specify
(S-CDE) Time performed
(S-CDE) Position during testing
(S-CDE) Devices in use during testing
(S-CDE) Pulse
(S-CDE) Pulse Regularity
(S-CDE) Systolic Blood Pressure
(S-CDE) Diastolic Blood Pressure

Sexual Function Data Set

Sexual Function Questionnaire Completed?
(S-CDE) Date and Time of Data Collection
(S-CDE) Interest in discussing sexual issues
(S-CDE) Sexual problems unrelated to spinal cord lesion
(S-CDE) If answered yes above, please specify:
(S-CDE) Sexual dysfunction related to the spinal cord lesion:
(S-CDE) [FEMALE-ONLY] Psychogenic genital arousal
(S-CDE) [FEMALE-ONLY] Reflex genital arousal
(S-CDE) [FEMALE-ONLY] Menstruation
(S-CDE) [MALE-ONLY] Psychogenic Erection
(S-CDE) [MALE-ONLY] Reflex Erection
(S-CDE) [MALE-ONLY] Ejaculation
(S-CDE) [BOTH] Orgasmic function

Quality of Life Data Set

Quality of Life Questionnaire Completed
(S-CDE) Date and Time of Data Collection
(S-CDE) Thinking about your own life and personal circumstances, how satisfied are you with your life as a whole in the past four weeks? Please use a scale ranging from 0 (completely dissatisfied) to 10 (completely satisfied). You can use 0 or 10 or any number in between.
(S-CDE) How satisfied are you with your physical health in the past four weeks? Please use a sccale ranging from 0 (completely dissatisfied) to 10 (completely satisfied). You can use 0 or 10 or any number in between.
(S-CDE) How satisfied are you with your psychological health, emotions and mood in the past four weeks? Please use a scale ranging from 0 (completely dissatisfied) to 10 (completely satisfied). You can use 0 or 10 or any number in between.
(S-CDE) I can keep up with my family responsibilities...
(S-CDE) I am able to do all of my regular family activities...
(S-CDE) I am able to socialize with my friends...
(S-CDE) I am able to do all of my regular activities with friends...
(S-CDE) I can keep up with my social commitments...
(S-CDE) I am able to participate in leisure activities...
(S-CDE) I am able to perform my daily routines...
(S-CDE) I can keep up with my work responsibilities (include work at home)...
(S-CDE) I am able to do all of the family activities that people expect me to do...
(S-CDE) I am able to do all of the family activities that I want to do...
(S-CDE) I am able to maintain my friendships as much as I would like...
(S-CDE) I can do everything for my friends that I want to do...
(S-CDE) I am able to do all of the activities with friends that people expect me to do...
(S-CDE) I am able to do all of the activities with friends that I want to do...
(S-CDE) I am able to do all of my regular leisure activities...
(S-CDE) I am able to do my hobbies or leisure activities...
(S-CDE) I am able to do all of the community activities that I want to do...
(S-CDE) I am able to do all of the leisure activities that people expect me to do...
(S-CDE) I can do all the leisure activities that I want to do...
(S-CDE) I am able to do all of the community activities that people expect me to do...
(S-CDE) I am able to go out for entertainment as much as I want...
(S-CDE) I am able to run errands without difficulty...
(S-CDE) I am able to do all of my usual work (include work at home)...
(S-CDE) I am accomplishing as much as usual at work for me (include work at home)...
(S-CDE) My ability to do my work is as good as it can be (include work at home)...
(S-CDE) I can do everything for work that I want to do (include work at home)...
(S-CDE) I am able to do all of the work that people expect me to do (include work at home)
(S-CDE) I am able to do all of my usual work...
(S-CDE) I am able to do all of the work that people expect me to do...
(S-CDE) I have to do my work for shorter periods of time than usual for me...
(S-CDE) I have trouble meeting the needs of my family...
(S-CDE) I have to limit my regular family activities...
(S-CDE) I feel limited in my ability to visit friends...
(S-CDE) I feel limited in the amount of time I have to visit friends...
(S-CDE) I have to limit the things I do for fun at home (like reading, listening to music, etc.)...
(S-CDE) I have to limit my hobbies or leisure activities…
(S-CDE) I have to do my hobbies or leisure activities for shorter periods of time than usual for me...
(S-CDE) I have to limit social activities outside my home...
(S-CDE) I have trouble keeping in touch with others...
(S-CDE) I have to limit the things I do for fun outside my home...
(S-CDE) I am doing fewer social activities with groups of people than usual for me...
(S-CDE) I have trouble doing my regular chores or tasks...
(S-CDE) I am limited in doing my work (include work at home)...
(S-CDE) I have to do my work for shorter periods of time than usual for me (include work at home)...

(S-CDE) I am limited in doing my work...
(S-CDE) I felt uneasy...
(S-CDE) I felt nervous...
(S-CDE) Many situations made me worry...
(S-CDE) My worries overwhelmed me...
(S-CDE) I felt tense...
(S-CDE) I had difficulty calming down...
(S-CDE) I had sudden feelings of panic...
(S-CDE) I felt nervous when my normal routine was disturbed...
(S-CDE) I felt fearful about my future...
(S-CDE) I felt anxious...
(S-CDE) I worried about my physical health...
(S-CDE) I felt like I needed help for my anxiety...
(S-CDE) I was easily startled...
(S-CDE) I felt fidgety...
(S-CDE) I felt something awful would happen...
(S-CDE) I felt worried...
(S-CDE) I suddenly felt scared for no reason...
(S-CDE) I worried about dying...
(S-CDE) I felt shy...
(S-CDE) I had difficulty sleeping...
(S-CDE) I had trouble relaxing...
(S-CDE) I felt depressed...
(S-CDE) I felt hopeless...
(S-CDE) I felt that nothing could cheer me up...
(S-CDE) I felt that my life was empty...
(S-CDE) I felt worthless...
(S-CDE) I felt unhappy...
(S-CDE) I felt I had no reason for living...
(S-CDE) I felt that nothing was interesting...
(S-CDE) I felt helpless...
(S-CDE) I felt that I wanted to give up on everything...
(S-CDE) I felt that I had nothing to look forward to...
(S-CDE) I withdrew from other people...
(S-CDE) I felt that everything I did was an effort...
(S-CDE) I was critical of myself for my mistakes...
(S-CDE) I felt sad...
(S-CDE) I felt lonely...
(S-CDE) I felt discouraged about the future...
(S-CDE) I found that things in my life were overwhelming...
(S-CDE) I felt unloved...
(S-CDE) I felt pessimistic...
(S-CDE) I had trouble keeping my mind on what I was doing...
(S-CDE) I felt emotionally exhausted...
(S-CDE) I felt like I needed help for my depression...
(S-CDE) I had trouble enjoying things that I used to enjoy...
(S-CDE) I had trouble controlling my temper...
(S-CDE) It was hard to control my behavior...
(S-CDE) I said or did things without thinking...
(S-CDE) I got impatient with other people...
(S-CDE) I was irritable around other people...
(S-CDE) I was bothered by little things...
(S-CDE) I became easily upset...
(S-CDE) I was in conflict with others...
(S-CDE) I felt impulsive...

(S-CDE) People told me that I talked in a loud or excessive manner...
(S-CDE) I said or did things that other people probably thought were inappropriate...
(S-CDE) I felt angry...
(S-CDE) I suddenly became emotional for no reason...
(S-CDE) I felt restless...
(S-CDE) It was hard to adjust to unexpected changes...
(S-CDE) I had a hard time accepting criticism from other people...
(S-CDE) I was stubborn with others...
(S-CDE) I threatened violence toward people or property...
(S-CDE) I felt exhausted...
(S-CDE) I felt that I had no energy...
(S-CDE) I felt fatigued...
(S-CDE) I was too tired to do my household chores...
(S-CDE) I was too tired to leave the house...
(S-CDE) I was frustrated by being too tired to do the things I wanted to do...
(S-CDE) I felt tired...
(S-CDE) I had to limit my social activity because I was tired...
(S-CDE) I needed help doing my usual activities because of my fatigue...
(S-CDE) I needed to sleep during the day...
(S-CDE) I had trouble starting things because I was too tired...
(S-CDE) I had trouble finishing things because I was too tired...
(S-CDE) I was too tired to take a short walk...
(S-CDE) I was too tired to eat...
(S-CDE) I was so tired that I needed to rest during the day...
(S-CDE) I felt weak all over...
(S-CDE) I needed help doing my usual activities because of weakness...
(S-CDE) I had to limit my social activity because I was physically weak...
(S-CDE) I had to force myself to get up and do things because I was physically too weak..
(S-CDE) Are you able to get on and off the toilet?
(S-CDE) Are you able to step up and down curbs?
(S-CDE) Are you able to get in and out of a car?
(S-CDE) Are you able to get out of bed into a chair?
(S-CDE) Are you able to push open a heavy door?
(S-CDE) Are you able to run errands and shop?
(S-CDE) Are you able to get up off the floor from lying on your back without help?
(S-CDE) Are you able to go for a walk of at least 15 minutes?
(S-CDE) How much DIFFICULTY do you currently have standing up from an armless straight chair (e.g., dining room chair)?
(S-CDE) How much DIFFICULTY do you currently have sitting down on and standing up from a chair with arms?
(S-CDE) How much DIFFICULTY do you currently have moving from sitting at the side of the bed to lying down on your back?
(S-CDE) How much DIFFICULTY do you currently have standing up from a low, soft couch?
(S-CDE) How much DIFFICULTY do you currently have going up and down a flight of stairs inside, using a handrail?
(S-CDE) How much DIFFICULTY do you currently have walking on uneven surfaces (e.g., grass, dirt road or sidewalk)?
(S-CDE) How much DIFFICULTY do you currently have walking around one floor of your home?
(S-CDE) How much DIFFICULTY do you currently have taking a 20-minute brisk walk, without stopping to rest?
(S-CDE) How much DIFFICULTY do you currently have walking on a slippery surface, outdoors?
(S-CDE) How much DIFFICULTY do you currently have climbing stairs step over step without a handrail? (alternating feet)?
(S-CDE) How much DIFFICULTY do you currently have walking in a dark room without falling?
(S-CDE) I had a sense of well-being...

(S-CDE) I felt hopeful...
(S-CDE) My life was satisfying...
(S-CDE) My life had purpose...
(S-CDE) My life had meaning...
(S-CDE) I felt cheerful...
(S-CDE) My life was worth living...
(S-CDE) I had a sense of balance in my life...
(S-CDE) Many areas of my life were interesting to me...
(S-CDE) I was able to enjoy life...
(S-CDE) I felt a sense of purpose in my life...
(S-CDE) I could laugh and see the humor in situations...
(S-CDE) I was able to be at ease and feel relaxed...
(S-CDE) I looked forward with enjoyment to upcoming events...
(S-CDE) I felt emotionally stable...
(S-CDE) I felt lovable...
(S-CDE) I felt confident...
(S-CDE) I had a good life...
(S-CDE) My life was peaceful...
(S-CDE) I was living life to the fullest...
(S-CDE) In most ways my life was close to my ideal…
(S-CDE) I had good control of my thoughts...
(S-CDE) Even when things were going badly, I still had hope...
(S-CDE) Are you able to turn a key in a lock?
(S-CDE) Are you able to brush your teeth?
(S-CDE) Are you able to make a phone call using a touch tone key-pad?
(S-CDE) Are you able to pick up coins from a table top?
(S-CDE) Are you able to write with a pen or pencil?
(S-CDE) Are you able to open and close a zipper?
(S-CDE) Are you able to wash and dry your body?
(S-CDE) Are you able to shampoo your hair?
(S-CDE) Are you able to open previously opened jars?
(S-CDE) Are you able to hold a plate full of food?
(S-CDE) Are you able to pull on trousers?
(S-CDE) Are you able to button your shirt?
(S-CDE) Are you able to trim your fingernails?
(S-CDE) Are you able to cut your toe nails?
(S-CDE) Are you able to bend down and pick up clothing from the floor?
(S-CDE) How much DIFFICULTY do you currently have using a spoon to eat a meal?
(S-CDE) How much DIFFICULTY do you currently have putting on a pullover shirt?
(S-CDE) How much DIFFICULTY do you currently have taking off a pullover shirt?
(S-CDE) How much DIFFICULTY do you currently have removing wrappings from small objects?
(S-CDE) How much DIFFICULTY do you currently have opening medications or vitamin containers (e.g., childproof containers, small bottles)?
(S-CDE) Because of my illness, some people avoided me...
(S-CDE) Because of my illness, I felt left out of things...
(S-CDE) Because of my illness, people avoided looking at me...
(S-CDE) I felt embarrassed about my illness...
(S-CDE) Because of my illness, some people seemed uncomfortable with me...
(S-CDE) I felt embarrassed because of my physical limitations...
(S-CDE) Because of my illness, people were unkind to me...
(S-CDE) Some people acted as though it was my fault I have this illness...
(S-CDE) Because of my illness, I felt embarrassed in social situations...
(S-CDE) Because of my illness, I felt emotionally distant from other people...
(S-CDE) Because of my illness, people tended to ignore my good points...
(S-CDE) Because of my illness, I was treated unfairly by others...

(S-CDE) Because of my illness, I felt different from others...
(S-CDE) Because of my illness, I worried about other people's attitudes towards me...
(S-CDE) Because of my illness, I worried that I was a burden to other...
(S-CDE) Because of my illness, people made fun of me...
(S-CDE) I was unhappy about how my illness affected my appearance...
(S-CDE) Because of my illness, strangers tended to stare at me...
(S-CDE) I lost friends by telling them that I have this illness...
(S-CDE) Because of my illness, it was hard for me to stay neat and clean...
(S-CDE) I felt embarrassed about my speech...
(S-CDE) I avoided making new friends to avoid telling others about my illness...
(S-CDE) I tended to blame myself for my problems...
(S-CDE) People with my illness lost their jobs when their employers found out about it...
(S-CDE) I am bothered by my limitations in regular family activities...
(S-CDE) I am disappointed in my ability to socialize with my family...
(S-CDE) I am bothered by limitations in my regular activities with friends...
(S-CDE) I am disappointed in my ability to meet the needs of my friends...
(S-CDE) I feel that my family is disappointed in my ability to socialize with them...
(S-CDE) I am disappointed in my ability to meet the needs of my family...
(S-CDE) I feel that my friends are disappointed in my ability to socialize with them...
(S-CDE) I am disappointed in my ability to do things for my friends...
(S-CDE) I am disappointed in my ability to socialize with friends...
(S-CDE) I am disappointed in my ability to keep in touch with others...
(S-CDE) I feel that others are disappointed in my ability to do community activities...
(S-CDE) I am disappointed in my ability to do leisure activities...
(S-CDE) I am bothered by limitations in doing my hobbies or leisure activities...
(S-CDE) I feel that I am disappointing other people at work...
(S-CDE) I am disappointed in my ability to perform my daily routines...
(S-CDE) I am disappointed in my ability to work (include work at home)...
(S-CDE) I am bothered by limitations in performing my daily routines...
(S-CDE) I am disappointed in my ability to take care of personal and household responsibilities...
(S-CDE) I am bothered by limitations in performing my work (include work at home)...
(S-CDE) I am satisfied with my ability to do things for fun outside my home...
(S-CDE) I am satisfied with the amount of time I spend doing leisure activities...
(S-CDE) I am satisfied with how much of my work I can do (include work at home)...
(S-CDE) I am satisfied with my ability to do household chores or tasks...
(S-CDE) I feel good about my ability to do things for my family...
(S-CDE) I am satisfied with my ability to meet the needs of those who depend on me...
(S-CDE) I am satisfied with my ability to do things for my family...
(S-CDE) I am satisfied with my current level of activity with family members...
(S-CDE) I am satisfied with my ability to do things for my friends...
(S-CDE) I am happy with how much I do for my friends...
(S-CDE) I am satisfied with my current level of activities with my friends...
(S-CDE) I am satisfied with the amount of time I spend visiting friends...
(S-CDE) I am satisfied with my ability to do things for fun at home (like reading, listening to music, etc.)...
(S-CDE) I am satisfied with my ability to do leisure activities ...
(S-CDE) I am satisfied with my ability to do all of the leisure activities that are really important to me...
(S-CDE) I am satisfied with my ability to do all of the community activities that are really important to me...
(S-CDE) I am satisfied with my current level of social activity...
(S-CDE) I am satisfied with my ability to run errands...
(S-CDE) I am satisfied with my ability to perform my daily routines...
(S-CDE) I am satisfied with my ability to work (include work at home)...
(S-CDE) I am satisfied with my ability to do the work that is really important to me (include work at home)...
(S-CDE) I am satisfied with my ability to take care of personal and household responsibilities...
(S-CDE) I am satisfied with the amount of time I spend doing work (include work at home)...
(S-CDE) I am satisfied with the amount of time I spend performing my daily routines...

(S-CDE) I am satisfied with my ability to work...
(S-CDE) I am bothered by limitations in performing my work...
(S-CDE) keeping track of time (eg., using a clock)?
(S-CDE) checking the accuracy of financial documents, (e,g., bills, checkbook, or bank statements)?
(S-CDE) reading and following complex instructions (e.g., directions for a new medication)?
(S-CDE) planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?
(S-CDE) managing your time to do most of your daily activities?
(S-CDE) planning an activity several days in advance (e.g., a meal, trip, or visit to friends)?
(S-CDE) getting things organized?
(S-CDE) remembering where things were placed or put away (e.g., keys)?
(S-CDE) remembering a list of 4 or 5 errands without writing it down?
(S-CDE) learning new tasks or instructions?
(S-CDE) I made simple mistakes more easily...
(S-CDE) Words I wanted to use seemed to be on the "tip of my tongue"...
(S-CDE) I had to read something several times to understand it...
(S-CDE) I had trouble keeping track of what I was doing if I was interrupted...
(S-CDE) I had difficulty doing more than one thing at a time...
(S-CDE) I had trouble remembering whether I did things I was supposed to do, like taking a medicine or buying something I needed...
(S-CDE) I had trouble remembering new information, like phone numbers or simple instructions...
(S-CDE) I walked into a room and forgot what I meant to get or do there...
(S-CDE) I had trouble remembering the name of a familiar person...
(S-CDE) I had trouble thinking clearly...
(S-CDE) I reacted slowly to things that were said or done...
(S-CDE) I had trouble forming thoughts...
(S-CDE) My thinking was slow...
(S-CDE) I had to work really hard to pay attention or I would make a mistake...
(S-CDE) I had trouble concentrating...
(S-CDE) I had trouble getting started on very simple tasks...
(S-CDE) I had trouble making decisions...
(S-CDE) I had trouble planning out steps of a task...

Autonomic Dysfunction Following SCI Questionnaire Data Set

Was the Autonomic Dysfunction Following SCI Questionnaire Completed?
Date and Time of Data Collection
Level of Spinal Cord Injury (SCI)
If you know your severity/completeness, check one
If you know your American Spinal Injury Association Impairment Scale (AIS) grade, please check one
Please indicate any medications you are taking and dosage
If indicated Other, please specify
Amitriptyline Dosage
Baclofen Dosage
Ditropan/Oxybutinin Dosage
Gabapentin Dosage
Lyrica/Pregabalin Dosage
Midodrine Dosage
Tylenol Dosage
Dosage for medication indicated as Other
Do you have episodes of autonomic dysreflexia (AD) (a condition where blood pressure rises very fast, usually because of a painful stimulus below the level of your lesion, resulitng in symptoms such as headaches, sweating, and goosebumps)?
How often does AD occur during exercise?
How often does AD occur during bladder emptying?
How often does AD occur during your bowel routine?
How often does AD occur during sexual activity?

How often does AD occur as a result of other known stimuli?
How often does AD occur spontaneously due to unknown reasons?
If you have selected 'other known stimuli', please explain (e.g. prolonged sitting):
How often do you experience headaches?
How often do you experience excessive sweating above the level of injury?
How often do you experience goosebumps?
How often do you experience anxiety?
How often do you experience heart palpitations?
How often do you experience headaches during exercise?
How often do you experience excessive sweating above the level of injury during exercise?
How often do you experience goosebumps during exercise?
How often do you experience anxiety during exercise?
How often do you experience heart palpitations during exercise?
How often do you experience headaches during bladder emptying?
How often do you experience excessive sweating above level of injury during bladder emptying?
How often do you experience goosebumps during bladder emptying?
How often do you experience anxiety during bladder emptying?
How often do you experience heart palpitations during bladder emptying?
How often do you experience headaches during your bowel routine?
How often do you experience excessive sweating above level of injury during your bowel routine?
How often do you experience goosebumps during your bowel routine?
How often do you experience anxiety during your bowel routine?
How often do you experience heat palpitations during your bowel routine?
How often do you experience headaches during sexual activities?
How often do you experience excessive sweating abovce the level of injury during sexual activities?
How often do you experience goosebumps during sexual activities?
How often do you experience anxiety during sexual activities?
How often do you experience heart palpitations during sexual activities?
How often do you experience headaches due to other known stimuli?
How often do you experience excessive sweating above the level of injury due to other known stimuli?
How often do you experience goosebumps due to other known stimuli?
How often do you experience anxiety due to other known stimuli?
How often do you experience heart palpitations due to other known stimuli?
Please rate how headaches affect you during daily living
Please rate how sweating above the level of injury affects you during daily living
Please rate how goosebumps affect you during daily living
Please rate how anxiety affects you during daily living
Please rate how heart palpitations affect you during daily living
Please rate how headaches affect you during exercise
Please rate how sweating above the level of injury affects you during exercise
Please rate how goosebumps affect you during exercise
Please rate how anxiety affects you during exercise
Please rate how heart palpitations affect you during exercise
Please rate how headaches affect you during sexual activity
Please rate how sweating above the level of injury affects you during sexual activity
Please rate how goosebumps affect you during sexual activity
Please rate how anxiety affects you during sexual activity
Please rate how heart palpitations affect you during sexual activity
How often do you experience dizziness during the day?
How often do you experience light headednessduring the day?
How often do you experience blurred vision during the day?
How often do you experience nausea during the day?
How often do you experience weakness during the day?
How often do you experience confusion during the day?
How often do you experience fatigue during the day?

How often do you experience passing out during the day?
What usually triggers these symptoms (e.g. heat, change in position)?
How often do you experience dizziness during transfers from the bed to your wheelchair?
How often do you experience light headedness during transfers from the bed to your wheelchair?
How often do you experience blurred vision during transfers from the bed to your wheelchair?
How often do you experience naudsea during transfers from the bed to your wheelchair?
How often do you experience weakness during transfers from the bed to your wheelchair?
How often do you experience confusion during transfers from the bed to your wheelchair?
How often do you experience fatigue during transfers from the bed to your wheelchair?
How often do you experience passing out during transfers from the bed to your wheelchair?
How often do you experience dizziness after a meal?
How often do you experience light headedness after a meal?
How often do you experience blurred vision after a meal?
How often do you experience nausea after a meal?
How often do you experience weakness after a meal?
How often do you experience confusion after a meal?
How often do you experience fatigue after a meal?
How often do you experience passing out after a meal?
How often do you experience dizziness during or after exercise?
How often do you experience light headedness during or after exercise?
How often do you experience blurred vision during or after exercise?
How often do you experience nausea during or after exercise?
How often do you experience weakness during or after exercise?
How often do you experience confusion during or after exercise?
How often do you experience fatigue during or after exercise?
How often do you experience passing out during or after exercise?
Please rate how dizziness affects you during transfers
Please rate how light headedness affects you during transfers
Please rate how blurred vision affects you during transfers
Please rate how nausea affects you during transfers
Please rate how weakness affects you during transfers
Please rate how confusion affects you during transfers
Please rate how fatigue affects you during transfers
Please rate how passing out affects you during transfers
Please rate how dizziness affects you after a meal
Please rate how light headedness affects you after a meal
Please rate how blurred vision affects you after a meal
Please rate how nausea affects you after a meal
Please rate how weakness affects you after a meal
Please rate how confusion affects you after a meal
Please rate how fatigue affects you after a meal
Please rate how passing out affects you after a meal
Please rate how dizziness affects you during or after exercise
Please rate how light headedness affects you during or after exercise
Please rate how blurred vision affects you during or after exercise
Please rate how nausea affects you during or after exercise
Please rate how weakness affects you during or after exercise
Please rate how confusion affects you during or after exercise
Please rate how fatigue affects you during or after exercise
Please rate how passing out affects you during or after exercise
Conditions under which orthostatic conditions occur
Standing/Sitting Time
Is there anything that was not asked that you would like us to know?